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CONGENITAL AND FAMILIAL HEMOLYTIC DISEASE IN CHILDREN

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Congenital and familial hemolytic icterus, although familiar to the pediatrician, has still many points of clinical interest which have hitherto been insufficiently investigated. For this reason, we have considered it worth while to publish a few personal observations on this disease made since 1926 in a great number of cases divided among fourteen different families. This article will be limited to a commentary on the clinical features and the transmission of the disease, avoiding all unnecessary references and leaving aside known facts and historical reviews.

Our personal experience is too incomplete to allow us to draw definite conclusions on the analysis of results, on the pathogenesis, on the pathologic physiology and, above all, on the therapy of the disease.

The condition was first described by Hayem,[1] as splenomegalic icterus; it was investigated by Gilbert and his pupils [2] and was classed as a distinct clinical entity in 1900 by Minkowski.[3] In 1907 it was connected by Chauffard [4] with lowering of erythrocytic resistance; since that period it has been intensively studied by Fiessinger and his associates [5] and by Troisier and Huber under the appellation of congenital and

1. Hayem, G.: Presse méd. **1**:121, 1898.

2. Gilbert, A.; Castaigne, J., and Lereboullet, T.: Bull. et mém. Soc. méd. d. hôp. de Paris **17**:1052, 1900. Gilbert, A., and Chabrol, E.: Compt. rend. Soc. de biol. **68**:836, 1910; **69**:416, 1911; **71**:162, 1911.

3. Minkowski, O.: Ztschr. f. klin. Med. **55**:34, 1904; Verhandl. d. Kong. f. inn. Med. **18**:316, 1900.

4. Chauffard, A.: Bull. et mém. Soc. méd. d. hôp. de Paris **24**:1201, 1907.

5. Fiessinger, N.; Olivier, H. R., and Ramadier, F.: Presse méd. **41**:1718, 1933.

familial hemolytic icterus. The first successful therapeutic result was unquestionably obtained by Banti, in 1903. It frequently happens, as will be shown later, that there is no sign of icterus in the findings, and for this reason we prefer the designation congenital and familial hemolytic disease.

The number of cases on which our statistics are based serves to prove that this disease is more frequent than is sometimes supposed. Some of our patients had been treated for other troubles before we settled on the diagnosis, and we believe that hemolytic disease is frequently undetected even by competent clinicians.

CLINICAL OBSERVATIONS

1. *Onset and Manifestations.*—Hemolytic disease linked to a constitutional and hereditary defect exists at birth but is rarely detected at that time. True, there may be no noticeable symptoms at birth, but it should be remembered that congenital diseases or malformations have a certain evolutionary development which may be perceptible at an earlier or a later date. Nevertheless, we consider that with greater attention this disease could be more frequently diagnosed early in infancy, provided icterus is not considered as an inevitable symptom.

Our most interesting case in this report is that of a 4 month old baby sent to our hospital (Hôpital Hérold) with a diagnosis of leukemia, which was later altered. The child had intensive anemia with no icterus. In his first days he had had a slight generalized jaundice, and since that time the spleen had been found enlarged.

Philippe Cor., aged 4 months, was sent to the hospital from a clinic for infants with a diagnosis of leukemia. In the clinic the hypertrophy of the spleen had been noticed. The child was born at 8 months. The weight at birth was 2,400 Gm. In the maternity ward, splenomegaly was observed, and the child was given antisyphilitic treatment (arsphenamine). A few days after birth he showed slight icterus of short duration. The weight and motor and psychic development were normal.

Examination on admission to the hospital showed that the height was normal and the weight 5,750 Gm. The complexion was pale and waxy. No subicterus was noted. The spleen was greatly enlarged and hard. Roentgen study gave normal findings. The red cell count was 3,130,000 and the hemoglobin content 60 per cent. The color index was 0.8. White blood cells numbered 25,000, of which polymorphonuclear neutrophils comprised 19 per cent, eosinophils 1 per cent, basophils 1 per cent, large mononuclears 7 per cent, medium mononuclears 66 per cent and lymphocytes 6 per cent. Granular red cells constituted 12 per cent. There were anisocytosis, poikilocytosis and marked polychromatophilia. The child's blood belonged to group 0 (14 of Moss). The bilirubin content, measured by the van den Bergh reaction, was 0.008 Gm. per liter, the calcium content 0.086 Gm. and the cholesterol content 0.7 Gm.

The child died from otitis a few days after his mother had removed him from the hospital.

On investigation of the family we found the mother (Marie Cor., aged 28) to have typical hemolytic disease; the symptoms were chronic

icterus, enlarged spleen, anemia, lowering of erythrocytic resistance, an organic mesocardiac murmur, periods of abdominal pain, fever and bilirubinemia (0.014 Gm. per liter, van den Bergh). The cholesterol content of the blood was 0.8 Gm. per liter. The mother also showed a markedly mongoloid facies, with malformation of the cranium (hyperostosis of the parietal and frontal bones, thickness of the cranial bones, deformation of the sella turcica and of the clinoid process).

Owing to numerous examinations and investigations, we have been able to determine under what conditions and at what age this disease is most often detected and which manifestation in children is the most significant. In regard to adults, we still lack data. The table summarizes data obtained by careful observation of 20 patients.

Diagnosis in Twenty Cases of Hemolytic Disease

Name	Age of Child When Disease Was First Diagnosed	Conditions Under Which Disease Was Diagnosed
Jack W.	12 years	Development of chronic icterus
Fred W.	14 years	Development of chronic icterus
Philippe Cor.	4 months	Symptoms of anemia and splenomegalia
Marie L.	9½ years	Acute febrile icterus
Jacques Mel.	9 years	Subicterus with anemia and splenomegalia
Jeanne Fr.	11 years	Splenomegalia
Georges Leb.	12 years	Hemolytic attack (crise de déglobulisation)
Luc M.	8 years	Hemolytic attack
Daniel Mon.	10 years	Hemolytic attack
Marie Th. M.	11 years	Chronic anemia with splenomegalia
Madeleine Bur.	14 years	Fatal hemolytic attack
Henri Bord.	8 years	Development of chronic icterus
François K.	4 years	Icterus and splenomegalia
Julien K.	4 years	Icterus and splenomegalia
Ida Ker.	4 years	Medical examination during investigation of family
Odette Leb.	7 years	Medical examination during investigation of family
Jean Tim.	3 years	Medical examination during investigation of family
Arlette Mat.	3 years	Medical examination during investigation of family
Madeleine M.	9 years	Medical examination during investigation of family
Henri M.	8 years	Medical examination during investigation of family

In all these cases the disease was detected between the ages of 4 months and 14 years. In 6 cases the patients had previously shown no suggestive symptoms, and it was due to investigation of the family in 1 case that the condition was detected in the other 5 at the respective ages of 3, 4, 7, 8 and 9 years. With each of the 6 children, the essential clinical symptom was excessive enlargement of the spleen. Four showed slight anemia and 2 a slight conjunctival subicterus which had not previously been noted.

Two other patients showed chronic anemia with splenomegalia, and 1 presented splenomegalia with no other symptom during a routine medical examination. In 7 cases icterus was the revealing symptom of the malady. Five of these patients had had chronic icterus from the respective ages of 14, 12, 8, 4 and 4 years. In 2 cases the disease was

diagnosed at the age of 9 years, during a passing attack of febrile icterus. In 4 cases it was a hemolytic attack which revealed the malady.[6] This serious form, which deserves a special study, will be described later. In 1 case the disease was discovered during a fatal attack in a child of 14 years.

With regard to the clinical onset and without reference to the disease in adults, we wish to draw the reader's attention to the following point:

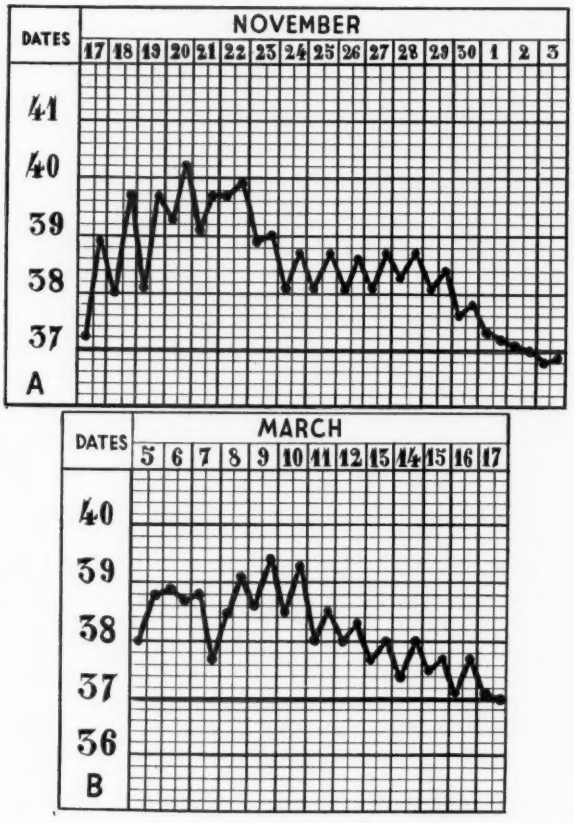

Fig. 1.—*A*, temperature chart (C.) made during a hemolytic attack in a 10 year old child with hemolytic disease. *B*, similar chart of an 8 year old child.

There have been cases in which hemolytic disease was undetected in childhood and adolescence, and discovered only when the patient, as an adult, underwent examination during or after an infectious illness. In this case, it is a mistake to consider hemolytic disease either as acquired during or as caused by this infection, a common error we shall refer to later.

6. Schrameck, S.: La maladie hémolytique, Paris, Amédée LeGrand, 1936.

II. *Symptoms and Manifestations: Their Frequency and Value.*—1. Icterus: Tradition considers this as a major symptom of a disease to which it has given its name. The majority of adults with the condition have a slight, pale yellow icterus coloring the skin and the mucous membranes. This form of jaundice is purely pigmentary, with no sign of retention of the biliary salts, bradycardia, pruritus or xanthelasma. The urine is clear and of normal color and quantity and usually contains an appreciable amount of urobilin. Bilirubin is found only after an attack of hemolysis. The feces remain normally colored and sometimes are even darker than normal. With variable intensity, according to the patient, icterus is more or less marked during the period of increased hemolysis. On the other hand, in some persons, chiefly in adults, icterus takes a different form; there are a darker tint and biliary retention, as with the type of chronic icterus caused by retention. In this case the icterus is caused by mechanical obstruction of the biliary channels due to secondary vesicular lithiasis.

We would particularly point out, however, the uncertain appearance of this icterus, which we found (merely as a mild form of subicterus in the majority of instances) in only 27 of the 37 cases on which our statistics are based. Ten of our patients showed no icterus, and at most a few could recall only occasional slight jaundice of short duration. The essential point is this: Absence of icterus is especially frequent in childhood; we have observed it eight times in children and twice in adults. Jaundice never shows in the first years, appearing only in children of school age or in adolescents or, even more frequently, in adults. Icterus frequently appears after a bout of fever caused by a so-called infection which proves to be in reality an acute hemolytic attack. Several such cases were observed. In the experience of the pediatrician, hemolytic disease is more commonly manifested by anemia than by icterus.

2. Anemia: This is a second symptom of regular occurrence, but it is well to know that in spite of pallor, actual anemia is usually slight, although sufficiently definite to be unmistakable. It adds to the jaundice a peculiar pale icterus which attracts the attention, leads to an examination of the mucous membrane and above all necessitates a blood count, the customary number of red blood cells varying between 3,500,000 and 4,000,000. It is unusual for the patient to have a permanently lower figure than 3,000,000 and we met with a lower number in only 1 case. The hemoglobin value runs parallel to the number of red blood cells, and the color index borders on 1.

The statement on the varying degrees of icterus also applies to anemia, and the various changes frequently even run parallel, both depending on the same hemolytic factor.

Another interesting detail is that anemia, although more frequent than icterus, has not proved to be an essential symptom. In 7 cases, the

red cell count remained consistently between 4,500,000 and 5,000,000. The finding of a normal number of red blood cells should not be a reason for setting aside the diagnosis of hemolytic disease.

3. Splenomegalia: This condition, on which Hayem, Gilbert and Minkowski laid special stress, is the major symptom as well as the one most constantly found. In all our 37 cases we found enlargement of the spleen, varying in intensity but always definite. Sometimes the spleen projected only 1 or 2 fingerbreadths beyond the floating ribs; at other times it attained considerable proportions, deforming the abdomen and spreading to the iliac crest. It usually retained a smooth surface, which was rarely uneven; it was often indurated and painless on palpation. It varied in size according to the intensity of anemia and icterus.

4. Adenomegalia: Another interesting and little known symptom is the swelling of the glands. Although not always present, it may sometimes figure among the clinical manifestations of hemolytic disease. In 2 cases were noted swellings the size of a small walnut; these were hard, smooth, painless and localized in the carotid, the axillar or the inguinal region. This glandular hypertrophy, detected in the absence of local infection in anemic subjects after a hemolytic attack, may be explained as the result of local metaplasia, i. e., transformation of the lymphoid tissue of the gland into myeloid tissue. Investigators, in particular Jordan,[7] have observed several examples of this metaplasia in cases of nonhemolytic anemia in adults.

During the course of hemolytic disease, erythropoietic reaction compensating hemolysis is not restricted to the bone marrow: Foci of extramedullar erythropoiesis have been detected on autopsy in the prevertebral region and in the hili of the kidneys. In our opinion—though we cannot be certain, as no biopsy was performed—these swellings are formed by heterotopic myeloid foci.

5. Cardiac Disturbances: The physician is frequently led to examine the cardiac region, his attention having been drawn to functional disturbances (dyspnea, palpitations, tachycardia) even in infants. A murmur may be detected either during a phase in the development of the malady, such as a severe attack of anemia, or between such episodes. This murmur, more noticeable at the base than at the apex, is apparently functional and does not imply a valvular lesion. However, as will be explained later, it is sometimes difficult to avoid making an error of diagnosis. But we wish to emphasize the possibility of serious cardiac complications.

A child of 15 years whose erythrocyte count did not exceed 2,000,000, showed symptoms of cardiac insufficiency, evidenced by distention

7. Jordan, H. E.: Extramedullary Erythrocytopoiesis in Man, Arch. Path. **18**:1 (July) 1934.

of the heart and an intermittent galloping sound. We had seen similar occurrences in 2 children with acute leukemia and severe anemia.[8] Laubry and Marchal and Soulié have mentioned analogous conditions in adults with anemia. We agree with them that it is a question of qualitative disturbance of the myocardial circulation connected with anoxemia.

6. Difficulties of Development; Dysmorphia, Infantilism: As is the case with the majority of chronic infantile diseases, hemolytic disease is a cause of difficulties of development; among some of our little patients these were particularly striking. Some children presented a peculiar infiltration of the tissues which may be explained as due to a disturbance of the water metabolism, though the figures of the blood proteins and the relative values of serum globulin and albumin were found to be normal. But the Volhard test applied to 2 patients revealed considerable delay in the elimination of water; this complication may have been linked with the splenohepatic hypertrophy, or it may have been of hypophysial origin. In favor of the latter pathogenesis is the fact that in both these cases the elimination of water became more normal under the influence of an injection of pituitary extract.

Difficulties of development were often observed. Some patients showed a definite retardation in height and weight: Jacques M., aged 9 years, weighed under 27 Kg.; Jean T., aged 12 years, was only 129 cm. in height. On comparison of several children of the same family, some of whom were diseased and others normal, this backwardness was even more noticeable. Jeanne Fr., aged 13, suffering from hemolytic disease, was 2 cm. shorter than her healthy 11 year old sister. In several children, backwardness of genital development was so marked that it could be described as infantilism; Hayem mentioned that these signs occurred in 2 cases.

Here again the part played by splenic hypertrophy deserves attention, as arrested development and infantilism have been observed in cases of splenomegalia. Freymann[9] and Curschmann[10] had several opportunities of observing a resumption of normal growth and sexual development after splenectomy. Should one agree with Naegeli[11] that the spleen has an inhibiting influence on general and sexual development and that this influence increases with hypertrophy and hyperfunction of the organ, or should one ascribe the inhibition to the influence of the hypophysis?

8. Debré, R.; Lamy, M.; Soulié, P., and Gabriel, P.: Bull. et mém. Soc. méd. d. hôp. de Paris **52**:991, 1936.

9. Freymann, G.: Klin. Wchnschr. **1**:2229, 1922.

10. Curschmann, H.: Deutsches Arch. f. klin. Med. **142**:79, 1923.

11. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, ed. 5, Berlin, Julius Springer, 1931; Deutsches Arch. f. klin. Med. **124**:221, 1917; Allgemeine Konstitutionslehre in naturwissenschaftlicher und medizinischer Betrachtung, Berlin, Julius Springer, 1927; Deutsche med. Wchnschr. **62**:797, 1936.

6. Ocular Lesions: Ocular complications rarely occur with hemolytic disease and do not seem to have been described or even mentioned, except briefly in a paper by Gännslen.[12] One of our patients, a girl aged 13, showed a white film of the cornea which took the shape of a wide horizontal strip almost filling the palpebral fissure (fig. 2*A*). The film was composed of nacreous, more or less concentric irregular spots, which seemed to project from the surface and gave the impression of being a

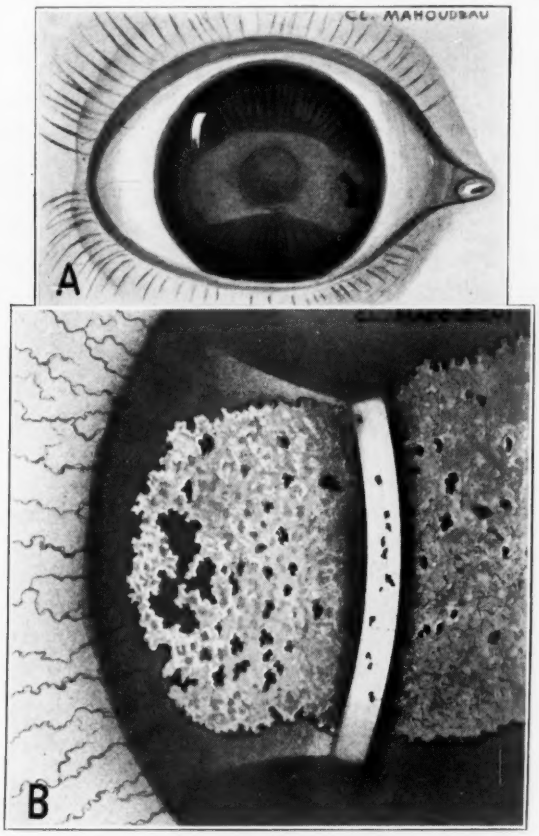

Fig. 2.—*A*, eye of Jeanne Fr., a 13 year old child with hemolytic disease. A white film appears on the cornea in the form of a wide horizontal strip. *B*, the eye as it appeared on examination with a slit lamp. The irregular marks correspond with the deposits in the thickness of the cornea.

deposit. With the assistance of M. J. Renard, who also associated this lesion with hemolytic disease, we made a special study of the phenomenon. With the use of a slit lamp, the epithelium was found to be intact;

12. Gännslen, M.: Deutsches Arch. f. klin. Med. **140**:210, 1922; Klin. Wchnschr. **6**:929, 1927; **9**:1308, 1930.

the seat of the lesion was in the thickness of the cornea, mainly filling the deeper part in the vicinity of Descemet's membrane. The limbus was not involved; it was separated from the film by a normally transparent band of the type seen in arcus senilis. The opaque portions were formed by irregular polygonal spots; these were tightly packed together, leaving occasional transparent areas. At certain angles, iridescence was visible, proving the probable existence of crystals (fig. 2 *B*). Without chemical analysis one can only form a hypothesis as to whether these

Fig. 3.—Twins with hemolytic disease. Observe in each the size of the abdomen and the craniofacial deformity, which gives a peculiar, Asiatic aspect.

crystals consisted of mineral salts, ferric pigments, or acid fat. Whatever the exact nature of this lesion, for which no effectual treatment was found, it represented a serious complication, spreading until this patient completely lost the sight of that eye.

8. Skeletal Deformity: This has been emphasized by several investigators, especially by Gännslen, who appears to have exaggerated its frequency. There were 4 instances of the condition in our cases. Two 4 year old univitelline twin boys presented marked deformities of the

bones, which in each case involved the head, including the face. The lesions were identical in the two children, giving them a striking aspect. The cranium of each boy was enlarged and brachycephalic. The high vertical forehead and the absence of an orbicular process suggested oxycephalia. The face was wide, with prominent cheek bones. The eyes were wide apart, with narrow horizontal palpebral fissures; they were slightly oblique, but there was no genuine epicanthus. Nevertheless, the face had a peculiar, almost Asiatic aspect. The middle and the lower level presented other anomalies. The palatal processes of the upper maxilla joined on a level with and at an acute angle to the median line. The result was a deformity of the roof of the palate, which was markedly ogival, and of the superior alveolar wall, which instead of being horizon-

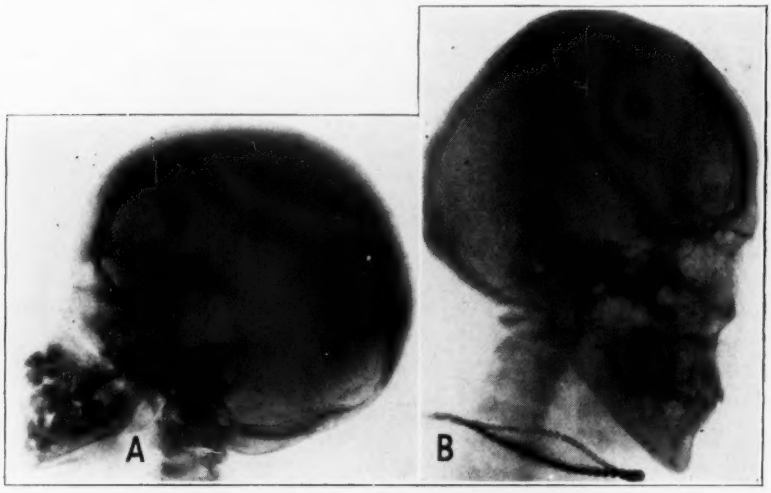

Fig. 4.—*A*, considerable thickening of the cranial wall in a child with hemolytic disease; note the brushlike appearance. *B*, thickening of the cranial wall in an adult with hemolytic disease.

tal formed a concave inferior curvature. This deformity prevented any union between the upper and the lower teeth as in addition each boy was slightly prognathous.

The cranial deformity was particularly noticeable. An excessive thickening of the roof of the skull, principally caused by a radiating deposition of the calcium, gave the skull the singular form associated with Cooley's anemia, as described as brush-shaped cranium *(crâne en brosse)*. These skeletal deformities may be considered a consequence of hyperactivity of the bone marrow, a hyperactivity compensating for the exaggerated destruction of red blood cells, which are fragile on account of their abnormal constitution. Two explanations may be offered for these skeletal anomalies: On the one hand, excessive proliferation of

the elements of the marrow would cause a tendency to a diversion or destruction of the osseous tracts, resulting in secondary hypertrophy of the bone; on the other hand, the excessive irrigation of the bone with blood would cause a premature symphysis of the cranial sutures; this would explain the heightening of the cranium and the oxycephalic deformity. These deformities were of the same nature as those observed with other diseases in which erythrocytic fragility appears to be a fundamental factor, such as Cooley's anemia or sickle cell anemia. Probably the seriousness of the skeletal deformity is in immediate relation to the degree of hemolysis and the extent of compensatory reaction of the bone marrow. The diffused character and the seriousness of the osseous modifications are conceivable in cases of Cooley's anemia, with which hypertrophic reaction of the marrow is excessive and is manifested by a high degree of erythroblastosis. Hemolytic disease being of lesser gravity, the red cells are less fragile, and the erythroblastic reaction of the marrow is less intensive. This will explain the uncertain appearance and unimportance of osseous deformities in cases of hemolytic disease.

Two adult patients examined with the assistance of M. Marcel Mignon manifested anomalies of the bones of the cranium: One showed a reduced anteroposterior diameter, which caused noticeable brachycephalia; in addition, the vertical diameter from the base of the occipital fossa to the vertex was far greater than normal. The thickness of the cranial walls was excessive, being 12 to 13 mm. instead of less than 10 mm., the normal thickness. The facial bones were slightly prognathous, with overdevelopment of the inferior maxilla, of which the two rami were thickened.

Cranial deformity was still more marked in the other case. A perpendicular frontal bone and a high bregma gave the appearance of a tower-shaped cranium *(crâne en tour)*. But the condition could not be called genuine oxycephalia. In reality, as emphasized in a previous article, the principal factors of a roentgen syndrome of oxycephalia were not present (reduction of the volume of the sinus, the presence of digitaliform marks, a forcing in of the body of the sphenoid from top to base, which caused basilar lordosis). In addition, there was considerable hyperostosis of the parietal and frontal bones. Roentgen study showed the spongy tissues of the diploe to be as opaque as the vertical layers, the result being a remarkable density of the cranial wall.

M. Marcel Mignon was of our opinion that the different aspects noted both in children and in adults represent two different phases of the same process. The brush-shaped deformity observed in a child would result from a period of intensive hyperactivity of the marrow. Such a period is perhaps temporary and the resulting phenomenon transitional. It may be that succeeding alterations of the bone later

give rise to the picture observed in adults, which is characterized solely by the considerable thickening of the cranial walls associated with the oxycephalic deformity.

9. Various Malformations: It is common to find several different malformations in the same patient. Some investigators have observed various congenital deformities, such as those of the jaw, the fingers (polydactylia, brachydactylia), the eyes (microphthalmia, heterochromia of the iris) and the ears (deformity of the auricle, otosclerosis). Muscular dystrophies and psychoses of different types have been described,

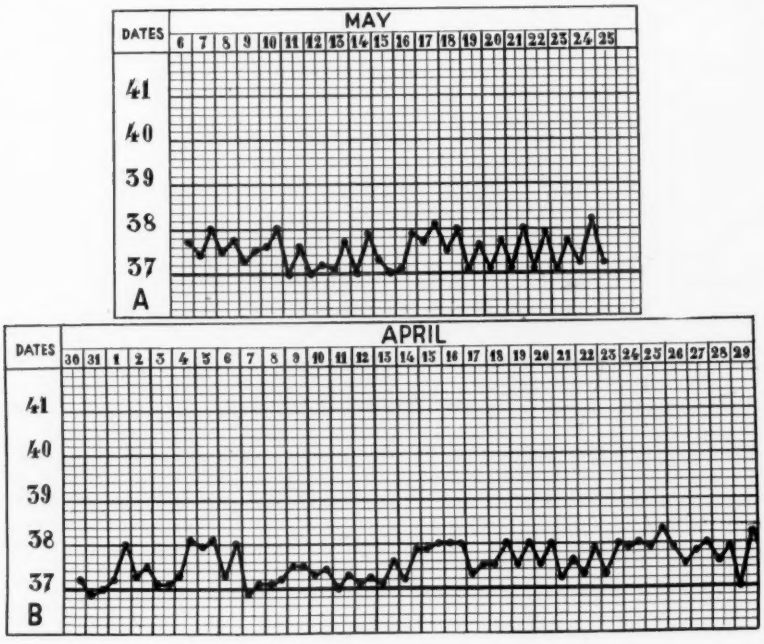

Fig. 5.—Temperature charts (C.) of children with hemolytic disease: *A*, chart of Jean Tim, aged 14 years; *B*, chart of Marie Thérèse Mar., aged 8 years.

as well as bronchiectasis. Personally, we have never come across any of these manifestations except slight prognathism, receding lower jaws or bad setting of the teeth, deformities not worth taking into account.

10. General Condition, Psychic Development, Fever: The patients' general condition varied, as will be pointed out, in the description of the course of the disease. The psychic development of our children was normal. They were rather sad and listless and were quieter than is usual at their age.

A rather remarkable feature of the disease is that fever is not unusual. Apart from that caused by incidental infection, which usually results from complications of the secondary vesicular lithiasis, there

were rises in temperature directly linked with the destruction of the blood cells. In addition to severe hemolytic attacks there were sometimes slighter attacks, with thermal elevation accompanying accentuation of the anemia. On three different occasions a child for several weeks had a temperature of 38 C. (101.4 F.) or over (fig. 2). A probable explanation for the high temperature in these cases may be that, aside from infection, there is excessive destruction of the blood proteins; similarly, fever accompanies resorption of effusions of blood.

OBSERVATIONS ON BLOOD, SERUM AND BONE MARROW

I. *Erythrocytes*—1. Number: It is unnecessary to dwell on the number of blood cells, but we may mention that when the anemia is of medium intensity the count oscillates as a rule between 3,000,000 and 4,000,000 and that an acute attack lowers the count to 2,000,000 and even to 1,000,000; the hemoglobin content runs parallel to the number of red cells, and the color index is therefore 1.

2. Dimensions and Morphology: Microcythemia has long been cited in connection with hemolytic congenital icterus. It has been rightly considered an important criterion. Our observations indicated that the diameter of the majority of the blood cells was much less than normal. About 75 per cent of the red cells have a diameter between 6 and 7 microns, instead of the normal diameter of 7.5 microns. Some authors (Adler,[13] Naegeli [11]) have maintained that the volume of erythrocyte, in spite of the decrease in diameter, is not inferior to that of a normal red cell, which would imply the morphologic anomaly of a peculiar, spheroid shape. The volumetric measurements that we attempted seemed to lead to so many errors that we dared not draw any definite conclusions.

3. Lowering of Resistance to Hypotonic Solutions: Chauffard [4] in 1907 mentioned the unusual fragility of the red cells in a hypotonic solution of sodium chloride. The truth of this statement has been confirmed several times since. The erythrocytes in the majority of our cases were particularly fragile. Normally, hematolysis starts with a 0.46 per cent solution, is definite with a 0.4 per cent solution and is complete in a 0.36 per cent solution. In several of our cases, hematolysis began at 0.6 or even 0.8 per cent. As did former investigators, we observed the double phenomenon of the lowering of the threshold and the lengthening of the geometric curve, two signs which go to prove that in certain persons erythrocytes are not all equally fragile. On the other hand, in other cases, cellular fragility was much less marked, hemolysis beginning with a 0.5 per cent solution. In 5 cases, the onset

13. Adler, A.: München. med. Wchnschr. **76**:454, 1929; **74**:2167, 1927; Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 34, 1922, p. 74.

of hemolysis occurred with a 0.56 per cent solution, i. e., the resistance was entirely normal. The Widal, Abrami and Brulé method of "deplasmatization" never succeeded in revealing erythrocytic fragility when the usual methods had failed.

However, we shall not jump to the conclusion that the red cells of subjects with hemolytic disease are neither of a particular species nor abnormally fragile; we believe only that there is no regular parallelism between the hemolysis seen in the course of the illness and that caused by the action of a hypertonic solution. We agree with Chabrol, who was the first to emphasize that the finding of normal erythrocytic resistance is not a reason for setting aside the diagnosis of hemolytic disease.

4. Reticulocyte Count: As first pointed out by Fiessinger in the course of his penetrating study on hemolytic disease, an increase in the number of reticulocytes can easily be shown by the use of vital stains. While in a normal subject the proportion is not more than 1 or 2 per cent, the figures usually varied between 8 and 20 per cent. We even noted toward the end of a hemolytic episode a count of 37 per cent. This increase is of great value in diagnosis.

5. Lesser Factors: Findings worthy of notice are polychromatophilia of red cells, the presence of a few nucleated erythrocytes and faint myelocytosis, all indicating regeneration of the blood.

The number of leukocytes is normal except during the hemolytic attacks; during their abatement the number has been known to increase to 20,000 or even 30,000.

II. *Serum.*—1. Hemolysins: Using a technic similar to that described by Troisier and Huber, we attempted several times to discover hemolysins in the plasma and in the serum of patients. Let us again stress the necessity of taking into consideration the type of blood and, that one may eliminate hemolytic action between different types, the importance of using only red cells of the same type as those of the patient or of type O (IV of Moss). On the other hand, certain precautions are necessary in searching for these hemolysins: For example, according to Hesser, the erythrocytes should be kept for a certain time on ice in order to increase their fragility.[14]

These methods may help to reveal the presence of lysins, but investigation is a delicate process which may easily lead to mistakes and is therefore not practical as an aid to correct diagnosis.

2. Bilirubinemia: The bilirubin content of the blood was determined for each patient by the use of the diazo reaction, either with van den Bergh's technic or with the method of Chabrol, Busson and Charonnat, that of the ring limit *(anneau limite)*. The first method produced

14. Debré, R.; Lamy, M., and Baudry, C.: Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1023, 1926.

regularly an indirect and delayed reaction. The figures were always above normal: 2, 4, and rarely 10 van den Bergh units; that is to say, 10, 20 and sometimes 50 mg. per liter of serum instead of the normal 0.2 to 0.6 unit (1 to 3 mg. per liter). The Chabrol technic gave 30 to 40 mg. and once as much as 110 mg., whereas with this technic the normal degree of cholemia is about 16 mg. per liter of serum.

3. Cholesteremia: In contrast to the increase of bilirubin, the proportion of cholesterol in the blood is nearly always lowered. It varies from 80 to 120 mg. per hundred cubic centimeters. The lowest figure met with was 70 mg. and the highest 140 mg.

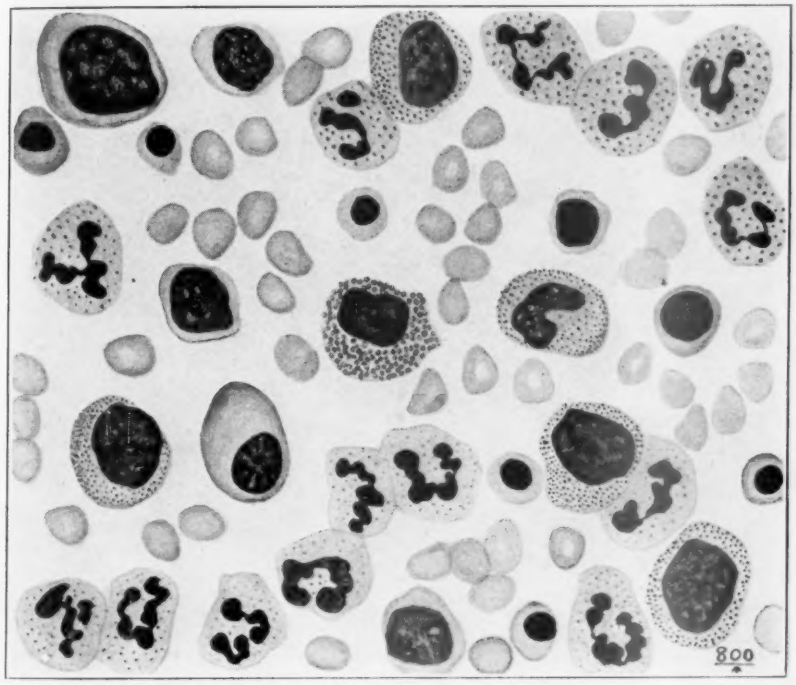

Fig. 6.—Normal bone marrow. Note the predominance of granular elements (polymorphonuclears, myelocytes, metamyelocytes). The erythroblasts (normoblasts) form about 15 per cent of the nuclear elements.

4. Bone Marrow: This was examined several times. Collected by Arikin's method of sternal puncture, the smears showed a definite erythroblastic reaction, the proportion of the nucleated red cells being between 30 and 50 per cent, instead of the normal 15 per cent.[15] The increase of nucleated erythrocytes in 1 case, in which there was only an

15. Debré, R.; Lamy, M., and Sée, G.: Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1712, 1935.

attenuated form of anemia, we consider extremely important, as it indicates that a hyperactivity of the marrow is characteristic of hemolytic disease (figs. 6 and 7).

5. Significance of Findings: These various serologic signs indicate a double process characteristic of the disease: hyperhemolysis and compensatory hyperactivity of the marrow.

We are of Chabrol's opinion that the increase of bilirubinemia is the most stable and the most significant sign of hemolysis. Among findings showing the importance of erythrocytic regeneration, special mention

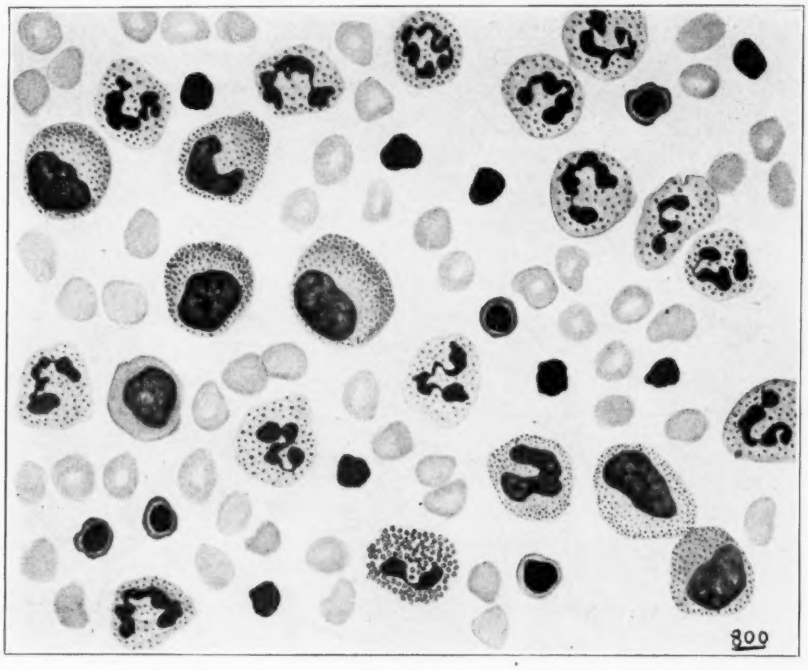

Fig. 7.—Bone marrow of a patient with hemolytic disease, showing the erythroblastic reaction. There are numerous normoblasts and bare nuclei of normoblasts (35 per cent of the nuclear elements instead of 15 per cent).

should be made of reticulocytosis, shown by analysis of the blood, and erythroblastic reaction, testified by myelograms.

COURSE; HEMOLYTIC ATTACKS

The slowness and mildness of the course of hemolytic icterus have always been emphasized. The condition was considered more troublesome than dangerous, with no influence on the expectancy of life. Acute attacks were looked on as a feature of acquired hemolytic icterus. Those averse to splenectomy still quote Chauffard's celebrated aphorism: "They

are more jaundiced than sick (ce sont plus des ictériques que des malades)." The histories of our patients prevent us from agreeing with this opinion.

Hemolytic disease proceeds by a succession of attacks, spaced at unequal intervals, which sometimes assume a serious character. These manifestations should not be ascribed to a clinically acquired form of the malady. In reality, they may occur in all types; moreover, we shall demonstrate how far a thorough and searching examination, made with a clear knowledge of the latent forms, may help one to distinguish between the acquired and the congenital forms of the disease.

The severe hemolytic attack is well known to the specialist but is often mistaken by the practitioner, who will tender a variety of diagnoses, such as acute meningitis, malignant endocarditis, typhoid fever, or malignant paludism. In short, as a general rule, he diagnoses the condition as an infectious disorder rather than as a disease of the blood.

The acute attacks are of four different types, characterized respectively by febrile jaundice, an abdominal syndrome, fever only and, lastly, superacute and eventually fatal anemia. A short description of each of these manifestations follows:

1. *Febrile Icterus.*—The child experiences a sensation of great lassitude, requiring rest in bed for some days. After a time and sometimes suddenly, jaundice, if already present, darkens, and the mucous membranes become discolored. Simultaneously the liver becomes slightly enlarged and tender. The left hypochondrium is also more or less painful, and the spleen grows larger and becomes sore. Fever is almost continuous, rising to 38 or 39 C. (100.4 or 102.2 F.). The patient has vertigo, palpitations and breathlessness at any effort and shows a systolic murmur on auscultation. The stools and the urine become darker. There is slight choluria. Laboratory examinations show anemia, an increase of cholesterol, a decrease in the erythrocytic resistance, granulated and nucleated red blood cells and involvement of the bone marrow.

The duration of the episode varies from a few days to some weeks. The spleen often continues to be larger and more painful than before, at least for a period; at the same time icterus and subicterus persist, varying in intensity.

2. *Abdominal Syndrome.*—This presents characteristic symptoms: The child is seized with violent, more or less localized abdominal pains and with frequent vomiting. In addition, he is tired and without appetite. As he has for some time experienced certain digestive disturbances, investigations will naturally be directed to the gastrointestinal tract, and if there is contraction of the abdominal wall possible appendicitis will be

considered. The painful and sudden character of these attacks may be due to the sudden tension of the hepatic and the splenic capsule.

3. *Periodic Fever.*—Some children may present only this symptom. Little Jeanne F. since the age of 18 months had had several sudden unexplained attacks of fever. After each attack the child was slightly jaundiced. The temperature rose to 39 or 40 C. (102.2 or 104 F.), but this had no serious effect, and the mother often noticed it only by chance. These attacks lasted two or three days and recurred every two or three months. Various diagnoses had been made. When the child was

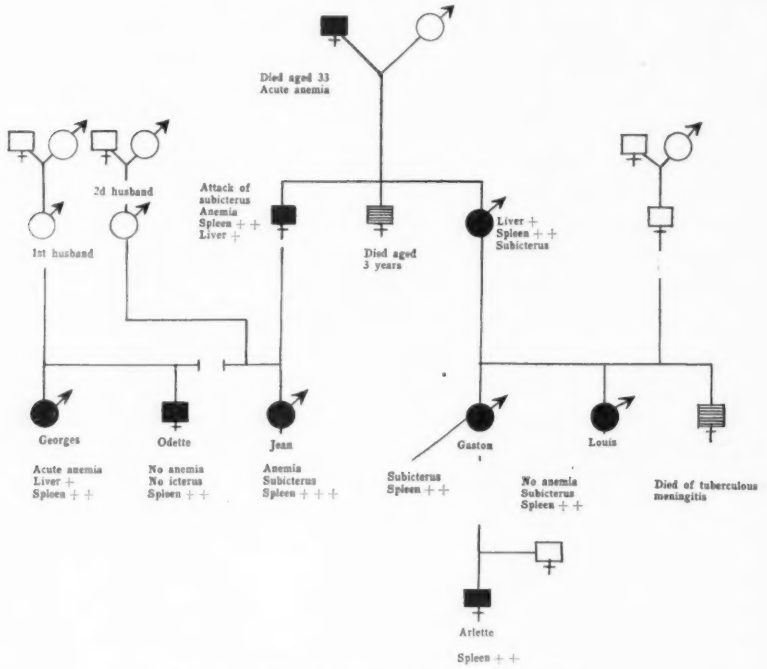

Fig. 8.—Genetic chart of the Mat. family.

brought to the hospital she was 11 years old. At that time the illness was diagnosed as familial hemolytic disease (the mother, Théodosie F., presented a typical form of the condition; fig. 9).

4. *Febrile Anemia.*—The real danger in this malady occurs when there is a severe attack of this type. The onset is sudden and occurs for no apparent reason, when the child is seemingly in good health. The temperature rises to 40 C. (104 F.) or more, and the fever is accompanied by severe tachycardia, vomiting and extreme prostration. These are the principal symptoms. Clinical examination reveals excessive splenomegalia, occasionally exaggerated and accompanied sometimes by hepatomegalia and always by a systolic murmur of anemic origin.

Anemia is excessive; the skin is discolored and the mucous membranes are bloodless. The number of red blood cells may fall to or below 1,000,000. In spite of their alarming character, these acute seizures of hemolysis rarely last more than two weeks; then apyrexia returns, and there is astonishingly rapid regeneration of blood cells (fig. 1).

Violent attacks of hemolysis are far from uncommon; their seriousness has been stressed by Lord Dawson of Penn, who cited 8 instances of death from acute anemia. When these manifestations take on a more serious form, the pulse quickens until it cannot be counted, the heart sounds become muffled, dyspnea is extreme and nervous symptoms (restlessness, loss of consciousness) precede death. Immediately before death the child has a cadaveric pallor. During the last moments of a

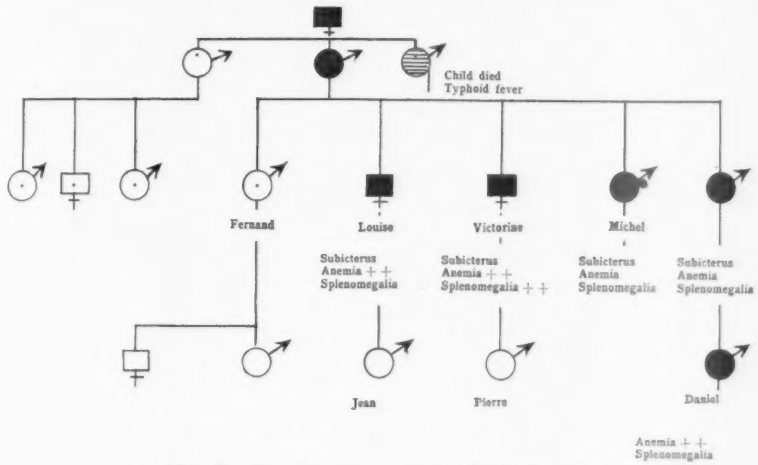

Fig. 9.—Genetic chart of the Mon. family.

child of 14 years, all these phenomena were present; Semelaigne reported a case in which the course was similar.

In our opinion, most investigators of this disease have underestimated its severity. We observed 2 deaths during acute attacks of hemolysis. Several sudden febrile paroxysms, attacks of jaundice and abdominal pains, sometimes with vomiting, were also noted.

Adding these serious symptoms to those of progressive anemia, of impaired development and of ocular complications, we find that a large enough number have been observed to prove the severity of hemolytic disease.

Death is rare; the disease is not incompatible with continued life. In fact, certain patients have lived to an advanced age, but the condition always remains a painful infirmity.

We have not discussed complications which are unknown in infants but sometimes develop when the patient is adult. Examples are vesicular

lithiasis, which occurs frequently in adults, and ulcers of the legs, which Eppinger has linked with hemolytic disease and which we encountered in the mother of 1 little patient.

CLINICAL TYPES

1. *Complete Type With Jaundice.*—Under this head can be classified cases in which occur all the important symptoms of the disease, viz., jaundice, anemia and splenomegalia. This type of involvement, though common in adult patients, is less frequent in children and in the aged. At least half of our observations were made on children who presented an incomplete type of the disease.

2. *Nonicteric Types.*—Of these unformed, stunted varieties two should be mentioned: the anemic and the splenomegalic.

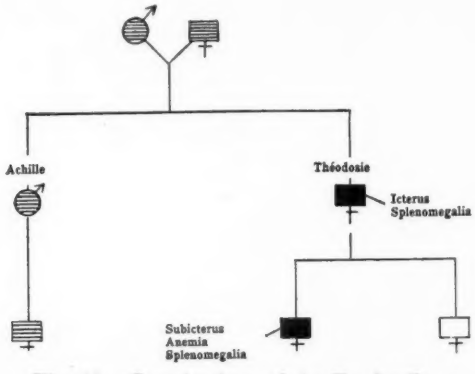

Fig. 10.—Genetic chart of the Fr. family.

The first appears in the form of chronic anemia with splenomegalia. The anemia may be moderate, the red cell count fluctuating between 3,000,000 and 4,000,000 with an occasional fall to 2,000,000 or even lower. At other times, a hemolytic attack may be suddenly aggravated by sudden fever, during the abatement of which there appears passing subicterus. Anemia is accompanied by splenomegalia of varying intensity.

In the second category, the illness, still more undeveloped, is characterized only by splenomegalia. That this is a fairly common type is shown by the frequency with which it may be detected during a systematic investigation of a family. Chauffard gave a good report on this point. We have observed several of these undeveloped types since 1926, more especially in young and in aged patients; Chabrol and Fiessinger have given a good description of the conditions. As a rule, they remain undetected or give rise to unfortunate errors which could have been avoided by careful inquiries into the family history. In reality, as we have just said, the traditional symptoms (lowering of erythrocytic resis-

tance, icterus) may be missing, which necessitates investigation of the family. The seriousness of these splenomegalic types should not be underestimated: They are susceptible of assuming all the grave complications of a complete form of the illness, especially acute attacks of hematolysis.

DIAGNOSIS

This is not the place to discuss the diagnosis; we wish only to emphasize the polymorphism of the disease, the large number of incomplete types and the numerous incidents that may occur, often with strange aspects, factors which go to explain the frequent failure to recognize the

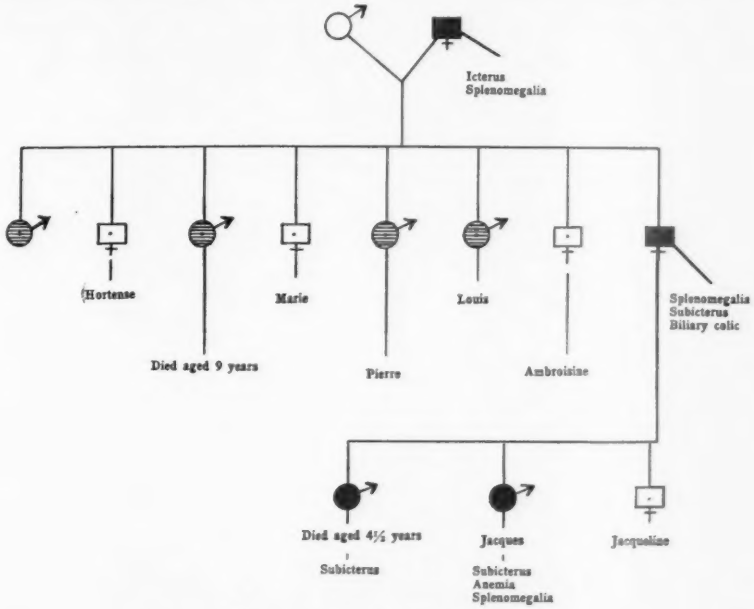

Fig. 11.—Genetic chart of the Mel. family.

disease. The periodic episodes, whether acute paroxysms or minor spells, often lead to the most regrettable errors, the diagnoses ranging from hereditary syphilis to kala-azar, appendicitis or endocarditis. Two points should be emphasized: the possibility of acute hemolytic anemia and that of acquired hemolytic icterus. In our opinion, certain conditions which are apparently acute hemolytic anemias of the Lederer or Brill type are in reality hemolytic attacks in patients suffering from congenital hemolytic disease. We cannot deny the existence of acute hemolytic anemia after observing 2 children with a syndrome which might well be classed in this category. But this diagnosis should be made only after investigation has disclosed no familial or constitutional defects and if no splenomegalia or hematologic stigmas persist after

the acute episode. Of 7 cases in which hemolytic attacks occurred, after inquiries of the families and prolonged observation of the patients 5 proved to be cases of constitutional hemolytic disease with periodic attacks.

We may also consider that many factors supposedly associated with acquired hemolytic icterus, as identified by Widal, Abrami and Brulé, belong in reality to congenital hemolytic disease. Neither the conditions under which acquired hemolytic icterus is first recognized, nor the accepted hematologic criteria allow a sure identification. A tardy onset of the disease by no means excludes a congenital origin. For example, 1 patient manifested icterus only at the age of 25, after high fever with splenomegalia; for the reasons just cited, the illness was mistaken for typhoid fever. In reality this was not an infectious condition but an

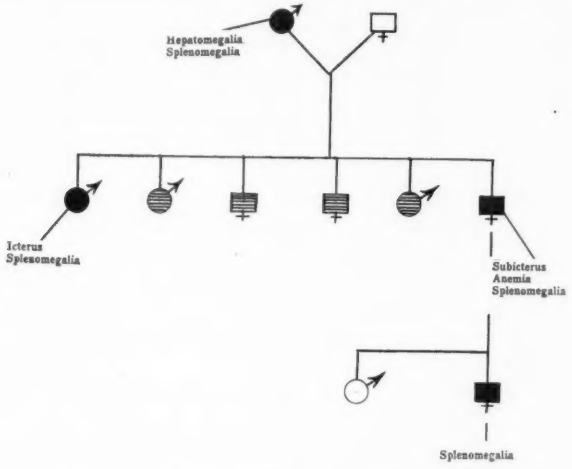

Fig. 12.—Genetic chart of the Ker. family.

acute febrile hemolytic episode followed, as is often the case, by subicterus. Proof of the constitutional and familial nature of the illness was given by the patient's son, who suffered from chronic anemia with splenomegalia and who showed all the clinical symptoms and the hematologic and serologic signs of hemolytic disease. Many times hemolytic jaundice which has supposedly developed as a sequel to an infection should in reality be considered as a manifestation of constitutional hemolytic disease. Circumstantial investigation into the family history, ascendant, collateral and descendant, will in most cases lead to the discovery of this fact.

CHARACTERISTIC FAMILIAL TRANSMISSION

The familial and hereditary characteristics of the malady were first emphasized by Hayem, Gilbert, Minkowski and Chauffard, and later by

Krannhals,[16] Meulengracht[17] and Guizzetti.[18] Hemolytic disease has been listed with the large group of constitutional and familial diseases.

Our statistics confirm the fact that hemolytic disease is transmitted, according to Mendel's law, as a dominant characteristic. This theory of the mendelian transmission of hemolytic defect was upheld by Campbell and Warner,[19] but as they could cite only 1 family and 15 cases their deduction cannot be considered as conclusive. Our observations included 83 persons belonging to 10 families, the majority of whom were examined and followed carefully during several years, some for ten years. Several families were able to furnish detailed information on 4 or 5 successive generations, and nearly all the living members of these families were examined. Leaving aside 24 whom we did not examine personally, of the remaining 59 persons 24 were immune and 35 were

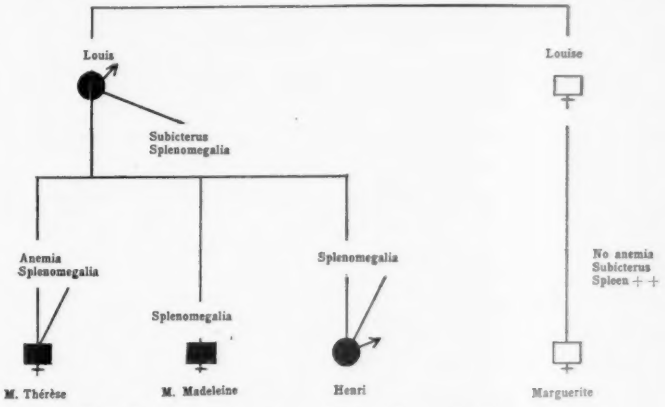

Fig. 13.—Genetic chart of the Mar. family.

diseased. On the other hand, by drawing up the family trees, the fact was brought to light that the disease was never transmitted to his or her descendants by a healthy member (figs. 7 to 13).

When about half of the children of diseased parents inherit the malady and, on the other hand, it is transmitted exclusively as a constant characteristic, the disease may be classed as belonging to a mendelian dominant type. These are the two main factors of the familial characteristics and the transmission of the disease which were revealed by our investigations.

16. Krannhals, V.: Deutsches Arch. f. klin. Med. **81**:596, 1904.

17. Meulengracht, E.: Deutsches Arch. f. klin. Med. **132**:285, 1920; **136**: 33, 1921; Der chronische hereditäre hämolytische Ikterus, Leipzig, W. Klinkhardt, 1922; Ugesk. f. læger **79**:883, 1917.

18. Guizzetti, P.: Beitr. z. path. Anat. u. z. allg. Path. **52**:15, 1911.

19. Campbell, J. M., and Warner, E.: Proc. Roy. Soc. Med. (Clin. Sect.) **15**:15, 1922; Quart. J. Med. **19**:333, 1926.

It is true that this study shows 60 per cent instead of 50 per cent inheritance of disease but figures can coincide with theoretic statistics only when large numbers are involved. The larger the number of observations, the nearer the statistics will be to the theoretic percentage, which is closely approached by our figure.

TREATMENT

No successful medical therapy for hemolytic disease has so far been discovered which can be admitted to be of the slightest value.

Splenectomy appears to be the only defense. Fiessinger and Bodin [20] formed this conclusion in 1927. The procedure was first performed by

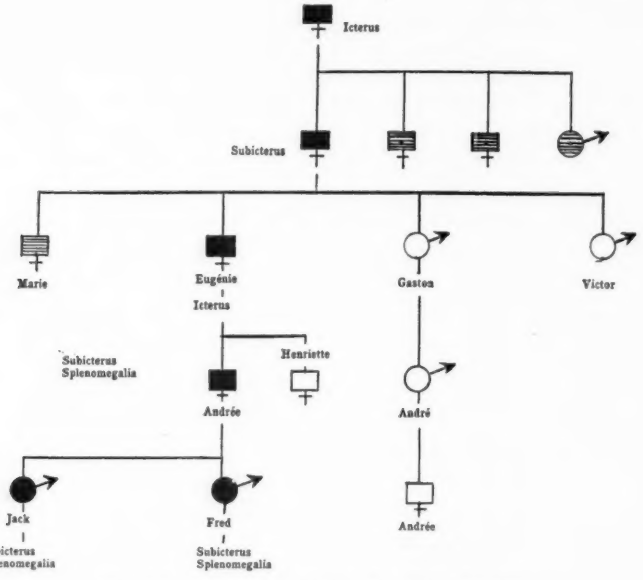

Fig. 14.—Genetic chart of the Wil. family.

Banti in 1903; since that date it has been repeated many times, with increasing success, as witnessed by statistics. In 1912 Gilbert, Chabrol and Bénard [21] had the operation performed on 3 patients. In 1914 [22] they listed 48 cases in which operaton was done; in 43 the procedure was successful, and in 5 the patients died. In 1926 Mayo published a report of 62 successful operations and 4 which were followed by death. Adding these numbers to those in recent publications, we calculate an operative

20. Fiessinger, N., and Bodin, P.: Presse méd. **35**:1297, 1927.

21. Gilbert, A.; Chabrol, E., and Bénard, H.: Compt. rend. Soc. de biol. **72**:161, 432 and 770, 1912.

22. Gilbert, A.; Chabrol, E., and Bénard, H.: Presse méd. **22**:21, 1914.

mortality of about 6.5 per cent. According to LeMaire, mortality tends to be higher with children, about 11.5 per cent.

Six of our 25 patients have undergone operation, 5 with success. The sixth was a child of 9½ years who, although the procedure was done under perfect conditions, died twenty-four hours later.

In spite of statistics which prove the progress in surgical technic, there still remain great risks in splenectomy. These risks must be weighed against those of allowing the disease to run its own course. In certain cases we definitely advise splenectomy, especially if the patient has had one or more acute hemolytic attacks or if anemia becomes chronic and progressive. The danger of accidents due to insufficiency of the cardiac valves is, to our minds, an additional reason, as are the statural and genital disturbances which, if the surgeon does not intervene, may lead to infantilism. It would therefore appear that splenectomy is advisable before puberty.

The operation has a striking influence over certain symptoms of the disease. Icterus and anemia both lessen rapidly. The development of the child improves progressively. Cholemia rapidly diminishes, but the reticulocyte count becomes normal only after several months. The cholesterol content of the blood mounts progressively, attaining sometimes a remarkably high value.

On the other hand, certain hemolytic stigmas persist. For instance, in many cases there is no definite modification in the fragility of the red cells. Microcytosis persists without alteration—the proof, some say, of hemolytic foci in the organism other than the spleen, or rather a proof that the blood defect is fundamental.

SUMMARY AND CONCLUSIONS

We report a number of cases of congenital and familial hemolytic disease in 14 different families, which we have observed since 1926, emphasizing the characteristics of the disease in children.

We draw attention to the instability, especially in children, of the traditional symptoms: icterus and lowering of erythrocytic resistance.

We indicate that anemia, although more frequent than icterus, may also be absent.

On the contrary, we have observed that splenomegalia seems to be present in every case.

We describe possible adenomegalia, a particular ocular lesion, peculiar deformities of the cranial bones, continuous fever and cardiac disturbances.

Among findings in the blood, we stress the certainty of reticulocytosis. We point out interesting characteristics of the bone marrow, which was obtained by sternal puncture.

We report on the characteristics of acute episodes which occur during the course of the illness (febrile icterus, abdominal syndrome, attacks of fever alone, violent and eventually fatal attacks of febrile anemia).

We emphasize the necessity of a thorough search for familial hemolytic disease when one encounters a case of so-called acquired hemolytic icterus.

We present charts to prove that the disease is a familial trait, transmitted according to Mendel's law as a dominant characteristic. This was observed by Campbell and Warner in 1 family; we observed 10 families, on several successive generations of which it was possible to obtain detailed information.

We concluded that splenectomy is the only effective therapy. With children it is often advisable before puberty.

NOTE.—Only the most important references have been cited. A complete list may be found in a recently published work by Gänsslen.[23]

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23. Gänsslen, M.: Die hämolytische Konstitution, in Cobet, R., and Gutzeit, K.: Neue Deutsche Klinik, Berlin, Urban and Schwarzenberg, 1936-1937, vol. 14, supp. 4, pp. 607-652.

ALTERED LIPID METABOLISM IN ACUTE INFECTIONS OF INFANTS AND OF OLDER CHILDREN

ALBERT V. STOESSER, M.D., PH.D.
MINNEAPOLIS

In previous communications [1] has been reported the influence of acute infections on the plasma lipid values of children ranging in age from infancy to 14 years. There was definite lowering of the values for total cholesterol, for total fatty acids and for phospholipids at the height of the disease as compared with the levels during convalescence. Diet had no demonstrable influence. Fever per se was not responsible for the lowering of the various lipid constituents of the blood plasma. Since experiments on animals have already shown that the lipids are involved in some way in the phenomena of immunity, further studies were made in order to furnish data which might be of value in more complete investigations into the chemistry of immunity. An analysis was made of the changes which occur in the free cholesterol and in the cholesterol esters and of the variations in the degree of unsaturation of the fatty acids of the blood fats and the plasma phospholipids.

MATERIALS AND METHODS

The cholesterol fractions and the iodine numbers, which indicated the degree of unsaturation of the fatty acids, were determined for a series of 24 hospital patients. There were 12 infants ranging in age from 3 to 13 months and 12 children ranging from 18 months to 13 years. Thirteen of the patients had rather extensive infections of the upper respiratory tract, and 11 were ill with pneumonia. The infants were given the routine milk formulas of the hospital every four hours or five times in twenty-four hours. During the height of the illness they did not take as much food as during convalescence. The older children received the ordinary mixed diets of the hospital. During the height of the infection they took a bland diet divided into three meals equally spaced, while during convalescence the full diet of the hospital was taken without difficulty.

During the period of observation little medication was given to the patients. The administration of fluid or blood subcutaneously, intramuscularly or intra-

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Presented at the Ninth Annual Meeting of the Society for Pediatric Research, Atlantic City, N. J., May 4, 1937.

1. McQuarrie, I., and Stoesser, A. V.: Influence of Acute Infection and of Artificial Fever on Plasma Lipoids, Proc. Soc. Exper. Biol. & Med. **29**:1281, 1932. Stoesser, A. V., and McQuarrie, I.: Influence of Acute Infection and Artificial Fever on the Plasma Lipids, Am. J. Dis. Child. **49**:658 (March) 1935.

venously was not permitted. The first sample of blood was obtained at the height of the disease and the second after the seventh day of convalescence.

The time at which each sample was collected was recorded, with the rectal temperature and the white blood corpuscle count. In many cases determinations of the hemoglobin content were also made, in order to check the factor of blood concentration. As far as possible the samples of blood were obtained under identical conditions as regards the time of day and the relation to meals. The majority of the samples were drawn between twelve and sixteen hours after a meal.

The blood was collected in specially cleaned tubes, and as soon as possible the plasma was separated from the cells by centrifugation. The plasma was quickly poured into the alcohol-ether mixture, and the various chemical analyses were made. Bloor's methods [2] were used to determine the values for blood lipids and for the total, the ester and the free cholesterol. The Rosenmund-Kuhnhenn method [3] as modified by Page, Pasternak and Burt [4] was used to determine the iodine absorption of the fatty acids of the serum. In spite of the precautions taken in drawing the blood, occasionally samples of plasma were tinged pink, which indicated hemolysis of some of the red blood cells. These specimens were all discarded, and fresh blood was obtained.

The behavior of the phospholipid fatty acids in relation to the variations in the phospholipids during acute infections of children was observed in 18 hospital patients ranging in age from 13 months to 15 years. Nine of the subjects had infections of the upper respiratory tract with acute otitis media, acute bronchitis or cervical adenitis, while the remaining 9 patients had pneumonia with no complications.

All the samples of blood obtained during and after the height of each infection were drawn between twelve and sixteen hours after a meal. In 8 of the cases the first sample was collected before the end of the second day of the febrile period of the disease, and in the remaining 10 cases, between the sixth and the seventh day of the illness. The second sample was collected from all children between the seventh and the ninth day of convalescence. Bloor's method [5] as modified by Boyd [6] was employed to obtain the total phospholipid content of the blood plsama, and the method of Page, Pasternak and Burt was again utilized to determine the iodine absorption values of the phospholipid fatty acids.

RESULTS

To conserve space and time the most important data have been condensed on the charts, which are largely self explanatory. They will

2. Bloor, W. R.: The Determinations of Cholesterol in Blood, J. Biol. Chem. **24**:227, 1916; Determination of Cholesterol Esters, ibid. **27**:107, 1916; The Determination of Small Amounts of Lipid in Blood Plasma, ibid. **77**:53, 1928.

3. Rosenmund, K. W., and Kuhnhenn, W.: Eine neue Methode zur Iodzahlbestimmung in Fetten und Olen unter Verwendung von Pyridinsulfatdibromid, Ztschr. f. Untersuch. d. Nahrungs- u. Genussmittel **46**:154, 1923.

4. Page, H. H.; Pasternak, L., and Burt, M. L.: Ueber den Transport von Fetten und Lipoiden durch Blut nach Oleingabe, Biochem. Ztschr. **223**:445, 1930.

5. Bloor, W. R.: The Oxidative Determinations of Phospholipid (Lecithin and Cephalin) in Blood and Tissues, J. Biol. Chem. **82**:273, 1929.

6. Boyd, E. M.: A Differential Lipid Analysis of Blood Plasma in Normal Young Women by Micro-Oxidative Methods, J. Biol. Chem. **101**:323, 1933.

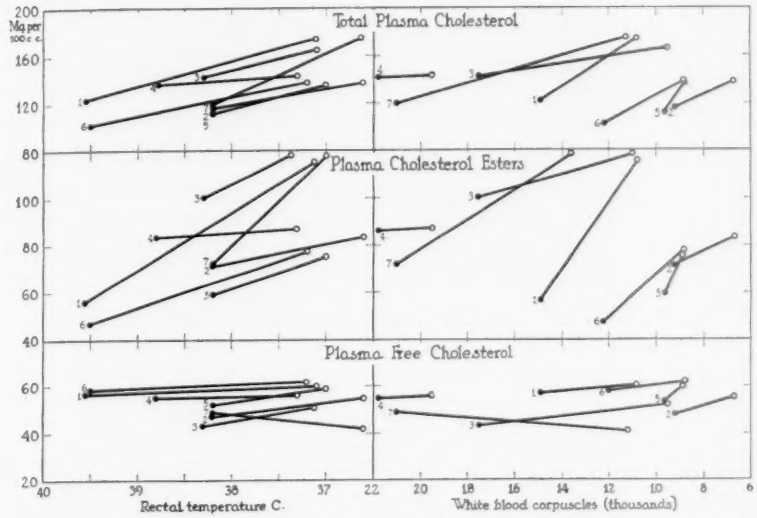

Chart 1.—The total cholesterol, the cholesterol ester and the free cholesterol content of the plasma in relation to the rectal temperature and to the white blood corpuscle count in 7 infants with acute infection of the upper respiratory tract. The solid dots represent the height of the disease and the open circles the period of convalescence.

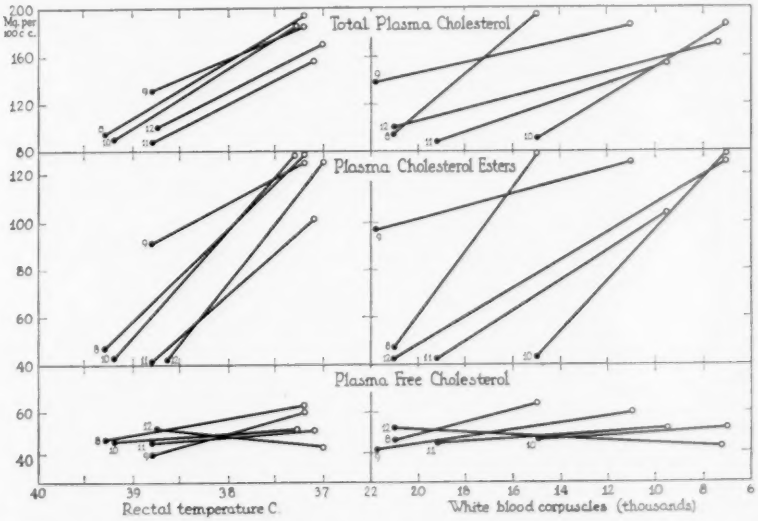

Chart 2.—The total cholesterol, the cholesterol esters and the free cholesterol content of the plasma in relation to the rectal temperature and to the white blood corpuscle count in 5 infants with pneumonia. The solid dots represent the height of the disease and the open circles the period of convalescence.

now be briefly considered in their natural order. In charts 1 and 2 are shown the results of the determinations of the cholesterol fractions made for the 12 infants with acute infections. The total cholesterol content of the plasma was low at the height of the disease. In the children with infection of the upper respiratory tract the total cholesterol value averaged 119 mg. per hundred cubic centimeters of plasma, while in the babies with pneumonia it was down to 99 mg. This low level was almost entirely due to a marked fall in the cholesterol ester content of the plasma. In the group with acute infection of the upper respiratory tract the cholesterol ester content dropped to an average of 69 mg. per hundred cubic centimeters of plasma, and in the patients with pneumonia the figure was as low as 51 mg. The free cholesterol content, on the other hand, was practically the same in both groups, the average values being 50 and 48 mg., respectively.

During convalescence a rather rapid recovery took place. The level of the total cholesterol rose in the infants with acute infection of the upper respiratory tract to an average of 155 mg. per hundred cubic centimeters of plasma. In the patients convalescing from pneumonia the value was up to 178 mg., which signified that in some of the babies the total cholesterol content was twice as high during convalescence as at the height of the acute illness. This increase in the total cholesterol value was the result of a great increase in the ester cholesterol. The average value for the patients with acute infection of the upper respiratory tract was 100 mg. per hundred cubic centimeters, and in the patients with pneumonia it rose to 122 mg. Associated with this marked rise in the ester cholesterol there was only a slight increase in the free cholesterol content, the average figure for both groups being 55 mg.

Charts 3 and 4 reveal the data collected from determinations made on the plasma of the 12 older children with acute infection of the upper respiratory tract and with pneumonia. While the average total cholesterol value was the same in both groups, being 129 mg. per hundred cubic centimeters of plasma during the height of the disease, the figure rose to 220 mg. in the first group and to 237 mg. in the second group during convalescence. This marked increase was produced by the cholesterol esters, which rose from the average low levels of 52 and 61 mg., respectively, to 143 and 162 mg. Little change was noted in the free cholesterol content. In fact, in some of the cases there was a slight decrease during the convalescent period.

The most marked changes in the cholesterol esters were noted in the older children, especially in the group with pneumonia. In the majority of the cases the lowest values for the total and for the ester cholesterol were found in the patients acutely ill with a high fever.

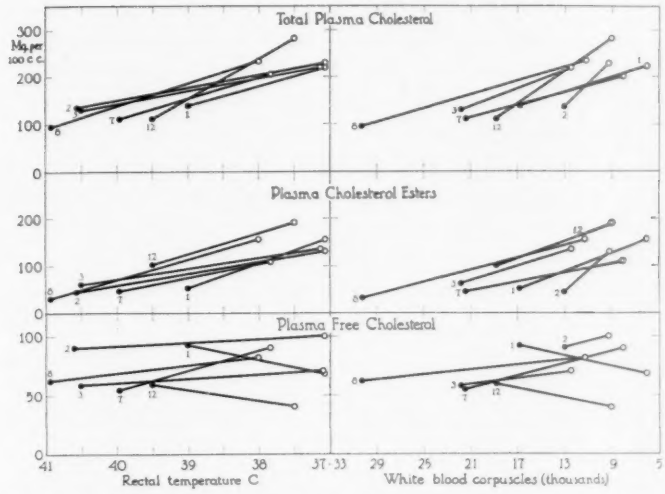

Chart 3.—The total cholesterol, the cholesterol ester and the free cholesterol content of the plasma in relation to the rectal temperature and to the white blood corpuscle count in 6 older children with infection of the upper respiratory tract. The solid dots represent the height of the disease and the open circles the period of convalescence.

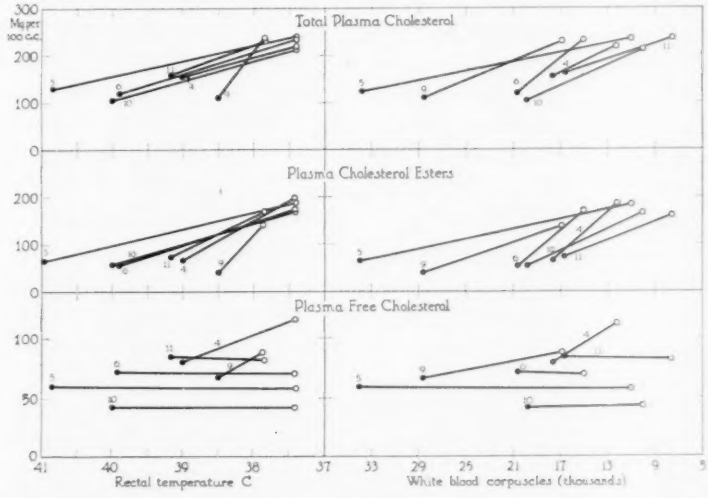

Chart 4.—The total cholesterol, the cholesterol ester and the free cholesterol content of the plasma in relation to the rectal temperature and to the white blood corpuscle count in 6 older children with pneumonia. The solid dots represent the height of the disease and the open circles the period of convalescence.

This observation was most common in the cases of pneumonia. Some of the children who appeared extremely toxic but whose temperature was only moderately elevated also had a low level of total and of ester cholesterol in their plasma. There was therefore no constant relation between the degree of fever and the extent of the fall in the level of the total or of the ester cholesterol. More irregular, however, was the change in the total and in the ester cholesterol value as compared with the rise and fall in the white blood cell count. The highest counts were not necessarily associated with the lowest cholesterol values. In some instances the leukocyte count continued to be elevated above the average range during convalescence, after the level of the cholesterol esters had returned to normal. In the majority of these cases an infection still existed, but this seemed to have little influence on the ester cholesterol content. It always rose rapidly soon after the temperature had dropped to normal and the patient had begun to regain his appetite and strength.

The results presented in charts 5 and 6 indicate the changes which occurred in the total fatty acids and the degree of unsaturation of the fatty acids during and after acute infections in infants. A fall in the content of the total fatty acid plasma took place during the height of the acute illness, and this was paralleled by a drop in the iodine absorption values. This signified in most instances that the iodine number of the fatty acids in the serum was definitely lower in the febrile period of the disease than during the period of recovery. During the height of the infection there may be a loss of unsaturated fatty acids, or the fatty acids may undergo desaturation. In the babies with acute infection of the upper respiratory tract, the total fatty acid content was at an average level of 346 mg. per hundred cubic centimeters of plasma during the acute illness and rose to 381 mg. in the period of convalescence. The associated iodine number was 90 in the febrile period, increasing to 102 during convalescence. The changes, however, were most marked and constant in the infants with pneumonia. In this group the total fatty acid content averaged 303 mg. per hundred cubic centimeters and rose to 363 mg., with a concomitant rise in the iodine number from 84 during the period of acute illness to 111 in convalescence.

The moderate drop in the content of the total fatty acids with the shift in the ratio of unsaturated to saturated fatty acids observed in the infants was also found to occur in older children. Charts 7 and 8 depict these changes during acute infections of the children. In the group with infection of the upper respiratory tract the total fatty acid content averaged 310 mg. per hundred cubic centimeters of plasma during the height of the illness and rose to 386 mg. in the convalescent period. This rise was accompanied by a change in the average iodine

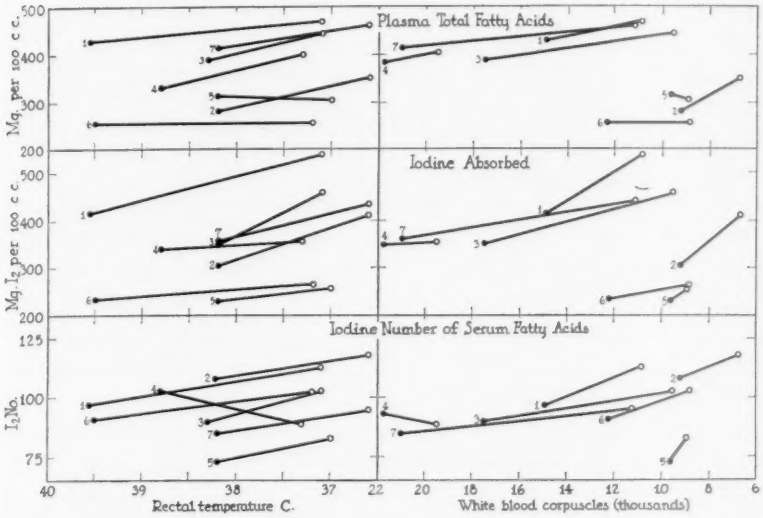

Chart 5.—The total fatty acid content of the plasma and the iodine absorption values and iodine numbers of serum fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 7 infants with acute infection of the upper respiratory tract. The solid dots represent the height of the disease and the open circles the period of convalescence.

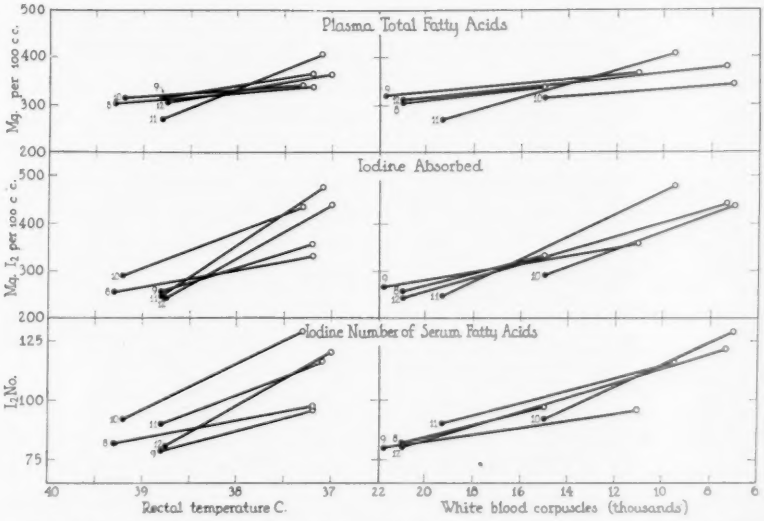

Chart 6.—The total fatty acid content of the plasma and the iodine absorption values and iodine numbers of serum fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 5 infants with pneumonia. The solid dots represent the height of the disease and the open circles the period of convalescence.

number from 96 to 118. The values did not differ much in the group with pneumonia. The total fatty acid content, from an average level of 307 mg. per hundred cubic centimeters of plasma with an iodine number of 96 in the febrile period rose to 375 mg. with an iodine number of 114 during convalescence.

The high temperatures occurring in the infants and older children were not necessarily accompanied by low values for the total fatty acids and for their iodine numbers, and slightly elevated temperatures at the height of some of the milder infections, such as those of the upper respiratory tract, were not an indication of small changes in the total fatty acids, especially as shown by the iodine absorption values. There was no constant relation between the height of the fever or the severity of clinical signs and the degree of saturation of the total fatty acids.

The total white blood corpuscle count varied inversely with the total fatty acid content of the blood plasma. The exceedingly high counts occurring during the height of the disease, however, were not all associated with the lowest iodine absorption values or with the lowest iodine numbers. In some instances only a slight increase in the leukocyte count during the febrile period was accompanied by a rather extensive drop in the unsaturation of the total fatty acids. Furthermore, the unsaturated fatty acids were slow in returning after the fever had subsided. Although the temperature might be normal for several days, the iodine absorption values still remained low. However, toward the end of the convalescent period the unsaturated fatty acids began to appear, and the iodine numbers then rose to values within the normal range. There was one exception. It is seen that in case 4, recorded on chart 5, the iodine number dropped to 88 in spite of the fact that the temperature was down to 37.3 C. (99.1 F.) at the time the sample of blood was drawn. This patient had had a mastoidectomy for an infection of the ear, and a purulent discharge was present in the wound. The white blood cell count was still elevated.

The behavior of the phospholipid fatty acids in relation to the variations in the phospholipids during acute infections of children is recorded on charts 9 and 10. For 8 of the infants and older children the first specimen of blood was obtained early in the infection, as suggested by Boyd.[7] There was, with only 2 exceptions, a fall in the plasma phospholipid values in this group of patients. The decrease in the serum phospholipids content was not accompanied with a fall in the iodine absorption values. On the contrary, the iodine numbers were higher than normal at this stage of the disease. With the phospholipids at an average level of 112 mg. per hundred cubic centimeters of plasma, the iodine number was 134. During convalescence the phospholipid content rose to 157 mg., and the iodine number fell to 101.

7. Boyd, E. M.: The Lipopenia of Fever, Canad. M. A. J. **32**:500, 1935.

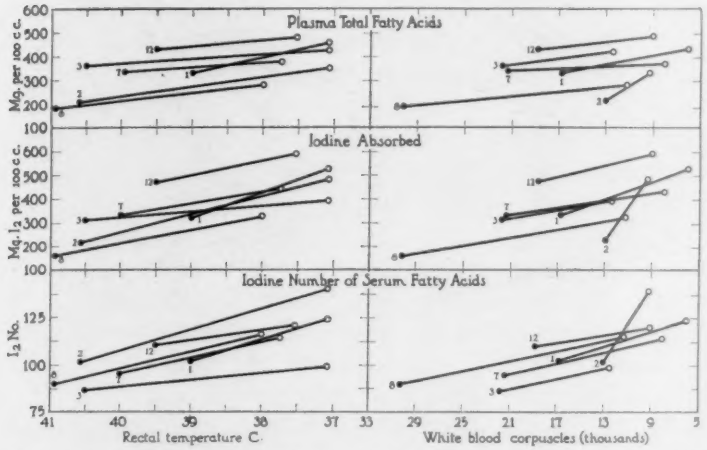

Chart 7.—The total fatty acid content of the plasma and the iodine absorption values and iodine numbers of serum fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 6 older children with infection of the upper respiratory tract. The solid dots represent the height of the disease and the open circles the period of convalescence.

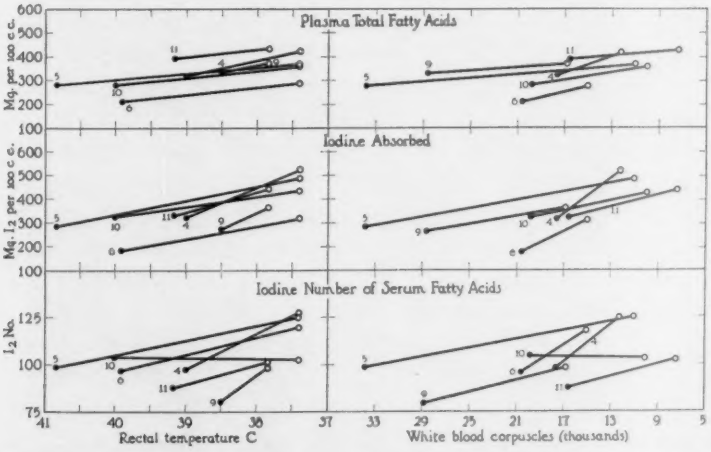

Chart 8.—The total fatty acid content of the plasma and the iodine absorption values and iodine numbers of serum fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 6 older children with pneumonia. The solid dots represent the height of the disease and the open circles the period of convalescence.

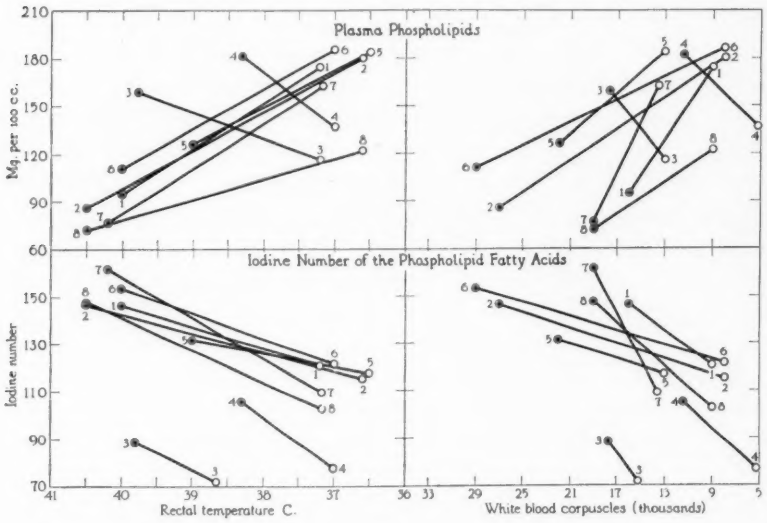

Chart 9.—The plasma phospholipid values and the iodine numbers of the phospholipid fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 8 infants and older children with infection of the upper respiratory tract and pneumonia. The solid dots in the circles represent the samples of blood collected on the second day of the febrile period and the open circles the samples obtained during the period of convalescence.

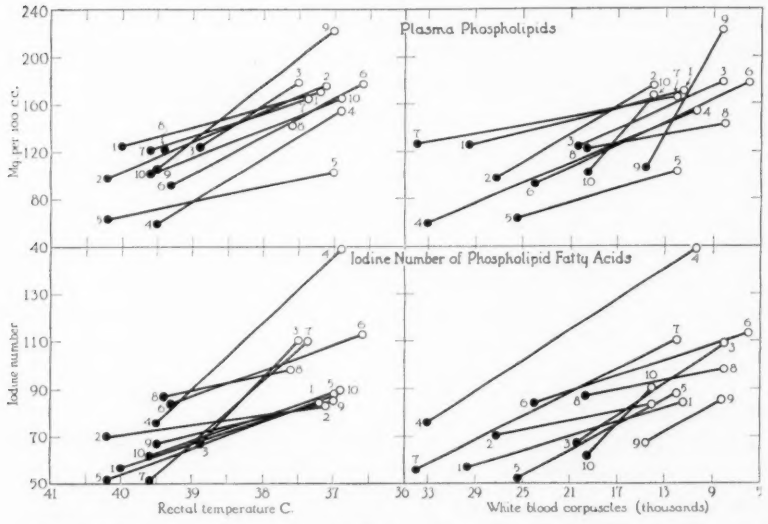

Chart 10.—The plasma phospholipid values and the iodine numbers of the phospholipid fatty acids in relation to the rectal temperature and to the white blood corpuscle count in 8 infants and children with infection of the upper respiratory tract and pneumonia. The solid dots represent the samples of blood collected on the sixth or seventh day of the febrile period or at the height of the infection and the open circles the samples obtained during the period of convalescence.

The plasma phospholipid values were consistently low in the other group of children, from whom the first specimen of blood was drawn toward the end of the height of the disease. This condition was accompanied by a marked fall in the iodine absorption values of the phospholipid fatty acids, which yielded low iodine numbers. The content of phospholipid fatty acids averaged 101 mg. per hundred cubic centimeters of plasma during the febrile period, when the iodine number was only 67. However, during convalescence the level of phospholipid fatty acids made a good recovery to an average figure of 165 mg., with an iodine number of 100.

Although the low level of the phospholipid fatty acids was maintained throughout the febrile period, the early rise in the iodine absorption values with the subsequent fall to extremely low values late during the height of the infection was most marked in the cases in which the temperature was very high. In these cases also the leukocyte count rose most rapidly early in the disease and remained high until a fall in temperature occurred. As a result, the highest white blood cell counts were found in the children who had the greatest iodine absorption values during the first few days of the infection and the most marked falls in the iodine number toward the end of the acute stage of the disease.

COMMENT

From the foregoing results it is certain that the various fractions of the plasma lipids are definitely altered during acute infections and that the abnormal values tend to change rather rapidly to normal after complete recovery from the disease. It has already been shown that diet and fever per se are not responsible for the lowering of the various lipid constituents of the blood plasma of subjects with acute infections. The determinations of the hemoglobin content of the blood which were made in the majority of the cases at the time the specimens of blood were drawn for study revealed that there was not much variation in any one instance, the hemoglobin values being so constant that changes in the blood concentration were considered to play little or no part in the results obtained.[8] Furthermore, the children were frequently weighed and carefully examined during the period of observation, and it was found that the acute illness did not produce any marked changes in the nutritional state. Malnourished children who contracted acute infection were not accepted for the investigation. As a result the low lipid values were not due to poor nutrition, as was observed in a series of cases by Man and Gildea.[9]

8. Man, E. B., and Gildea, E. F.: Variations in Lipemia of Normal Subjects, J. Biol. Chem. **119**:769, 1937.

9. Man, E. B., and Gildea, E. F.: Serum Lipoids in Malnutrition, J. Clin. Investigation **15**:203, 1936.

Although both Sperry [10] and Boyd [11] have shown that the total cholesterol values are generally exceedingly low in newborn infants, it was noted in the infants of this study that after the third month of life the lipids increased rapidly, usually reaching figures which were little below those obtained for older children. As the infants grew older there was less difference in the cholesterol values of the plasma between one subject and another. However, a small degree of variation continued throughout childhood, and this was in line with the observations of Schube.[12] He found that the blood cholesterol in different persons fluctuates along different patterns. There were a certain ebbing and flowing of the blood cholesterol, which was always within normal limits. Schube could not explain this, but attributed it to the unexplained occasional changes in the fat metabolism of some persons.

Offenkrantz and Karshan,[13] studying a large group of patients with various pathologic conditions from the neonatal period to the age of 12 years, obtained results from their determinations of cholesterol which revealed the maintenance of similar values for the two sexes, the trend toward a lower ester cholesterol value at the lowest age level and the lack of any sort of correlation between free or total cholesterol values and the percentage under or over normal weight. All these observations, according to these writers, point to a deeper meaning for variations in serum cholesterol values in children than merely that they result from given pathologic conditions. Nevertheless, in this study acute infections had a definite influence on the total cholesterol and the cholesterol ester content of the plasma, while the free cholesterol content remained practically unchanged.

There is a strong tendency for the ratio of esterified to free cholesterol to remain constant in the normal person.[14] Changes in the ratio, according to Sinclair,[15] are therefore of considerably greater clinical significance than changes in the level of the total cholesterol. The drop in the ratio which was found to occur in all the cases of this investigation is also considered to be a prominent feature of injury to

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10. Sperry, W. M.: Cholesterol of the Blood Plasma in the Neonatal Period, Am. J. Dis. Child. **51**:84 (Jan.) 1936.

11. Boyd, E. M.: Lipid Composition of Blood in Newborn Infants, Am. J. Dis. Child. **52**:1319 (Dec.) 1936.

12. Schube, P. G.: Variations in the Blood Cholesterol of Man Over a Time Period, J. Lab. & Clin. Med. **22**:280, 1936.

13. Offenkrantz, F. M., and Karshan, M.: Serum Cholesterol Values for Children, Am. J. Dis. Child. **52**:784 (Oct.) 1936.

14. Sperry, W. M.: Relationship Between Total and Free Cholesterol in Human Blood Serum, J. Biol. Chem. **114**:125, 1936.

15. Sinclair, R. G.: Fat Metabolism, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6.

the liver. Various interpretations have been suggested, such as deranged esterification in the liver, storage of esters in the liver [16] or faulty absorption from the intestines.

The moderate fall of the total fatty acid content of the plasma which occurs during acute infections of infants and older children is accompanied by a loss of the unsaturated fatty acids from the serum. The normal ratio of unsaturated to saturated fatty acids is greatly disturbed. This may be due to a temporary disarrangement in the physiologic processes of the liver, since this organ, which has been considered the center of fat metabolism, can under normal conditions desaturate fatty acids.[17] There is a high degree of unsaturation of the hepatic fatty acids. It is, however, difficult to determine definitely whether this high degree of unsaturation of the lipids in the liver is due to simple selection of the unsaturated acids on the part of the liver or whether desaturation actually takes place. Injury to the liver might lead to a decrease of unsaturated fatty acids in the blood plasma if the latter were true.

Tangl and Berend [18] and later Berend [19] claimed to have found a dehydrogenase in the pancreas which is capable of desaturating fatty acids to a considerable extent in a fairly short time. The suggestion has also been made that the saturated fatty acids are desaturated in the intestines and are thus rendered diffusible and capable of being absorbed. Acute infection could easily disturb this mechanism of absorption and thereby reduce the ability of the body to maintain the unsaturated fatty acids of the plasma at a proper level.

Increasing interest is being shown in the changes which the plasma phospholipids undergo during acute infections. Boyd [20] observed that normally only small variations occur in the phospholipid content of human blood plasma during the course of the day. On the other hand, he noted that during infection the concentration of phospholipids in the plasma rose temporarily with the onset of fever and then fell to subnormal values throughout the period of elevated temperature.[7] This may be important, in view of the statement of Sinclair [21] that a part of the phospholipids in the plasma serves as a means of transporting

16. Beumer, H.: Zur Frage der cholämische Lipämien und des Estersturzes, Jahrb. f. Kinderh. **146**:1, 1935.

17. Leathes, J. B.: A Lecture on the Functions of the Liver in Relationship to the Metabolism of Fat, Lancet **1**:593, 1909.

18. Tangl, H., and Berend, N.: Die Fettresorption durch die Desaturation der Fettsäuren, Biochem. Ztschr. **220**:234, 1930.

19. Berend, N.: Ueber ein fettdehydrierendes Ferment, Biochem. Ztschr. **260**: 490, 1933.

20. Boyd, E. M.: Diurnal Variations in Plasma Lipids, J. Biol. Chem. **110**: 61, 1935.

21. Sinclair, R. G.: Blood Phospholipid as a Transport Mechanism, J. Biol. Chem. **115**:211, 1936

fatty acids from the blood into the tissues, where they are burned. This circulating metabolic phospholipid, according to most recent investigations, does not accumulate to any extent in the various organs of the body, with the exception of the liver and possibly of the intestinal mucosa. It is not yet known where the plasma phospholipids are formed. The liver has been considered because it has a rapid phospholipid metabolism and considerable changes may occur in the amount of phospholipid.[22] There is, however, a still more rapid turnover of phospholipid in the intestinal mucosa [23] than in the liver, and although this has been used as evidence that the phospholipids serve as an intermediary stage in resynthesis of fat,[24] it may indicate that the phospholipids of both the blood plasma and the liver originate in the intestinal mucosa.

In spite of the strong tendency for the ratio of the saturated to the unsaturated fatty acid in the phospholipids to remain constant, acute infections produce rather marked changes in the iodine absorption values of the phospholipid fatty acids. Early in the disease there usually is a rapid increase in the iodine numbers of the fatty acids of the plasma phospholipids. The onset of fever probably is accompanied by a sudden flood of unsaturated fat from the depots into the blood stream, and the phospholipids pick up the unsaturated fatty acids with great avidity. On the other hand, the increase in the intensity of the fat metabolism during the febrile period might cause further unsaturation of the unsaturated fatty acids, the amount of unsaturated fatty acid remaining constant.

Toward the end of the febrile period of the illness, the iodine absorption values fall to low levels with a definite decrease in the phospholipid content of the plasma. The desaturation may be entirely due to the rapid utilization of the unsaturated fatty acids by the altered metabolic processes present during an acute infection. There is, however, an additional factor which could play a rather significant role. The observation has been made that certain toxic substances, such as cobra venom, when mixed with lecithin cause it to lose its unsaturated fatty acid radical.[25] The resulting lecithin compound contains a

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22. Stoesser, A. V.; McQuarrie, I., and Anderson, J. A.: Effects of Various Diets, Cholesterol and Choline on Liver Lipids of the Rat, Proc. Soc. Exper. Biol. & Med. **33**:595, 1936.

23. Sinclair, R. G., and Smith, C.: The Turnover of Phospholipids in the Intestinal Mucosa, J. Biol. Chem. **121**:361, 1937.

24. Sinclair, R. G.: The Metabolism of the Phospholipids: The Passage of Elaidic Acid into Tissue Phospholipids; Evidence of the Intermediary Role of Liver Phospholipid in Fat Metabolism, J. Biol. Chem. **111**:515, 1935.

25. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry, Baltimore, Williams & Wilkins Company, 1931, vol. 1.

relatively high proportion of saturated fatty acids. The question thus arises as to whether the bacterial toxins of an acute infection could have the same influence on the plasma phospholipids. Most logical at the present time is the assumption that the intensity of fat metabolism during an acute infection and the presence of the bacterial toxins in the blood may both be responsible for the ultimate fall in the plasma phospholipids to abnormal levels with an associated extensive loss or desaturation of their unsaturated fatty acids. Should this actually be found to occur, it would give the phospholipids an important part in the phenomena of immune reactions.

Goodner and Horsfall [26] have studied the relation of the lipids to agglutination and precipitation in immune reactions. They found that the removal of lipids from the type I antipneumococcus horse serum causes a loss of the visible phenomena of type-specific agglutination and precipitation and in the case of rabbit serum a marked reduction in these properties. Initial activity of the type-specific antibody can be restored to extracted horse serum by the addition of lecithin and to rabbit serum by the addition of cephalin. Therefore the phospholipids have already been shown to play a definite role in specific immune reactions. Further investigations may broaden their significance in immunity.[27]

SUMMARY AND CONCLUSIONS

Previous studies have shown that there is a definite lowering of the values for total cholesterol, total fatty acids and phospholipids at the height of acute disease as compared with the levels during convalescence. In these studies diet had no demonstrable influence, and fever per se was not responsible for the lowering of the various lipid constituents of the blood plasma.

A still more thorough study of the plasma lipids was made in the hope of revealing at least in part the mechanism of resistance of the host to an acute infection. Forty-two infants and children with acute infection of the upper respiratory tract and with pneumonia were selected.

The lowering of the total cholesterol level during an acute illness was found to be due to a marked fall in the ester cholesterol content.

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26. Goodner, K., and Horsfall, F. L.: The Protective Action of Type I Antipneumococcus Serum in Mice: The Effect of Added Lipids on the Protective Mechanism, J. Exper. Med. **64**:369, 1936; Properties of the Type Specific Proteins of Antipneumococcus Sera, Immunochemical Fractionation of Type I Antipneumococcus Horse and Rabbit Sera, ibid. **66**:413, 1937.

27. Landsteiner, K., and Chase, M. W.: Immunochemistry, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1937, vol. 6.

The values of cholesterol esters rapidly returned to the normal range when the infection had subsided. The free cholesterol content of the blood serum underwent little change.

The relation between the degree of fever and the extent of the fall in the ester cholesterol level was not constant. Furthermore, the highest white blood cell counts were not necessarily associated with the lowest cholesterol values.

The moderate drop in the total fatty acids in acute infections was accompanied by a definite lowering of the iodine absorption values; this resulted in an iodine number of the serum fatty acids which was significantly lower during the febrile period of the illness than during the afebrile period of convalescence. The iodine absorption value did not readily return to within the normal range until the patients had fully recovered and there was no residual infection.

No constant relation existed between the height of the fever or the severity of clinical signs and the degree of saturation of the total fatty acids. The leukocyte counts varied inversely with the total fatty acid content of the blood plasma. The extremely high counts occurring during the height of the disease were not all associated with the lowest iodine absorption values.

In the majority of the cases at the onset of the infection the decrease in the phospholipid content of the serum which occurred during the febrile period of the disease was accompanied by a rise in the iodine absorption values for the phospholipid fatty acids. This rise was followed by a marked fall, so that toward the end of the height of the illness low iodine numbers were obtained for the fatty acids of the phospholipids.

The intensity of the fat metabolism during an acute infection and the presence of the bacterial toxins in the blood may be responsible for the fall in the plasma phospholipids to abnormal levels with associated extensive loss of their unsaturated fatty acids. This assumption gives the phospholipids an important part in the phenomena of immune reactions.

GIARDIASIS IN CHILDREN

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Giardia lamblia belongs to the flagellates. Its name has often been changed; some clinicians still call it Lamblia intestinalis. The parasite can be found in every part of the world. A number of similar species in animals have been described, but it is still a question whether the mouse or the rat can be a host of the type of Giardia found in human beings. The incidence of the parasite was estimated at 12 per cent in the United States by Hegner and at about 10 per cent in Hungary by Lörincz.[1] The infection is more common among children than among adults.

Giardia lamblia has a vegetative and a cystic stage. The vegetative form is pear shaped, about 14 microns in length and 8 microns in diameter, with two symmetric sides. Each side has a nucleus and four free flagella. The axostyle is crossed by a typical parabasal body. The organism adheres to the epithelial cells of the intestine by the aid of a concave peristome. No products of metabolism or foreign corpuscles can be seen in the body of Giardia; nourishment probably takes place through osmotic processes. Multiplication occurs by binary fission in the long axis. The vegetative form of the organism usually lives in the duodenum or in the upper part of the ileum. The cysts, measuring about 7 by 11 microns, are passed with the feces. The mature form has a thick wall and contains four nuclei and a network system.

Organisms in the vegetative form are easily found in the duodenal fluid. They seldom appear in the feces, except in case of severe diarrhea. Diagnosis can be made by the cysts which appear in the stools in practically every case. Before examination, feces must be diluted with physiologic solution of sodium chloride. Some practice is needed, but determination can be made easier by certain methods of concentration. Ferrous hematoxylin is used for staining. No successful method of cultivation is known at present. Morphologic and biologic details of Giardia will not be discussed here, since data can be found in the extensive literature of parasitology.

From the Pediatric Clinic of the Royal Hungarian Peter Pázmány University.

All the fecal examinations were controlled by the Department of Parasitology of the State Hygienic Institute of Hungary. Dr. George Makara, chief of the department, gave advice and assistance.

1. Lörincz, F.: Parasitology, Budapest, 1936.

The pathogenicity of Giardia has been discussed for many years. Previous investigators (Nothnagel;[2] von Jaksch;[3] Joachim[4] and others) held that it is perfectly harmless. First Grassi and Schewiakoff[5] and then Perroncito[6] accused it of sometimes causing diarrhea. Opinions are still diverse, but the majority of authors have expressed the belief that Giardia is pathogenic. One of the questions is in what percentage of the infected can symptoms be found. According to Brumpt,[7] of 10 infected persons only 1 has symptoms. Others estimated the rate higher. According to the opinion expressed by Behnke,[8] Landázuri,[9] Gross[10] and others Giardia is only relatively pathogenic: Its presence may aggravate an already existing illness, or, with its virulence augmented, the heretofore harmless parasite may excessively increase in number and thus become a cause of disease. Papers on giardiasis are fairly numerous, especially in the Latin countries. A detailed bibliography can be found in the works of Behnke[8] and Champsaur.[11]

Symptoms of giardiasis have been described as follows: After infection the illness begins with mild or severe symptoms. After a short period of incubation, nausea, spasms and tenesmus appear, and diarrheal stools are mingled with blood and pus, as with violent dysentery. The temperature is usually normal. In some cases the signs may imitate those of acute appendicitis. Acute symptoms abate in a few days, and the disease enters a chronic stage. This period is the one in which the disease is usually observed. Sometimes only mild signs follow the infection, such as headache, dull pains over the region of the epigastrium and sensations of hunger after eating, accompanied by one or two watery stools (Tsuchiya and Andrews[12]). Even such complaints may be lacking, with symptoms no more serious than dizziness, migraine and slight loss of power leading to the chronic period.

Duodenitis, colitis, rectosigmoiditis and, above all, hepatic disorders were observed in the chronic stage. Many authors stated that they found Giardia in the B bile, and many expressed the opinion that, especially in the cases of incurable, obstinate involvement, the parasite lives

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in the gallbladder and the bile ducts (Chantriot;[13] Cade, Morénas and Grivet;[14] Garin, Bernay and Desgeorges;[15] Labbé,[16] and others). As secondary symptoms of giardiasis several authors (Champsaur;[11] Silvestrini[17] and others) mentioned loss of weight and anemia, but no systematic investigations have been made in this line. Even anemia resembling the pernicious type was described as a result of giardiasis (Garin[18]).

Most authors stated that symptoms are rare in the chronic stage, the number of "healthy carriers" being estimated as high as 80 to 90 per cent. Most of the examinations were made on adults; there have been few systematic observations on children. The usual point of investigation has been the rate of infection among diseased persons and not the incidence of disease among the infected. (Sangiorgi[19] succeeded in finding the flagellate in 25 per cent of cases of diarrhea, Porter and Fantham[20] in 14 per cent and Kennedy and Rosewarne[21] in 12 of 136 cases.)

Therefore the questions to be answered were these: What is the exact percentage of the diseased among the infected children; what are the symptoms, and what is the effect of the parasite on the so-called healthy carriers? These problems I tried to solve. Of course, all my statements and findings, which result from investigations carried out in Hungary, may pertain to the disease in Hungary alone. I cannot claim that they are valid in other countries, not knowing whether the various strains of Giardia agree in biologic properties with those living in Hungary.

The observations were made partly on patients of the Children's Clinic of the Budapest University and partly on children inhabiting a village near Budapest. All in all, 1,391 children between the ages of 2 and 17 years were examined for parasites. Diagnosis was made in every instance by the aid of fecal examination. One hundred and fifty-five children proved to be infected by Giardia lamblia, the youngest of them being 2½ years of age and the oldest 17. The index of infection was about the same in boys and in girls. Detailed particulars regarding age and the infection index are given in table 1.

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SUBJECTS

Of the 155 infected children, only 144 could be precisely examined. For each a detailed past and present history was recorded, physical examination was made and the height and weight were measured. In addition to tests for tuberculosis and syphilis, which were carried out in every instance, careful roentgen and electrocardiographic examinations and detailed laboratory tests (urinary and blood analyses, tests for gastric, hepatic and renal function and for sugar and fat metabolism and determination of ferments and fermentative processes) were made in the great majority of the cases in order to eliminate the possibility that causes other than Giardia were responsible for the condition. These examinations led to the elimination of 32 children who gave evidence of various other diseases and pathologic conditions (vitium cordis, tuberculosis, pleuritis, chronic nephritis, diabetes, epilepsy, tumor of the brain, helminthiasis), and 20 more had to be left out because of their positive reaction to tuberculin. (Among the 144 children, 43 showed a positive reaction on intradermal injection of old tuberculin in dilutions ranging from 1:10,000 to 1:250. Of these, 10 children were not

TABLE 1.—*Number of Examined and of Infected Children According to Age and Sex*

Age, Years		Boys		Girls		Total	
		No.	%	No.	%	No.	%
2-5	Examined	186		135		315	
	Infected	8	4.4	8	5.9	16	5.1
6-9	Examined	280		295		575	
	Infected	39	13.9	42	14.2	81	14.1
10-13	Examined	181		156		337	
	Infected	21	11.6	24	15.4	45	13.3
14-17	Examined	60		104		164	
	Infected	6	10.0	7	6.7	13	7.9
Total	Examined	701		690		1,391	
	Infected	74	10.6	81	11.7	155	11.1

excluded, since they were over 13 years of age and showed no increase in the rate of sedimentation. Thirteen of the others were excluded because of diseases such as those just mentioned.) It should be pointed out that many of the complaints and symptoms of the children who were omitted were similar to those of the others. Twenty-one children harbored intestinal parasites which might be suspected of causing symptoms (7, Ascaris; 14, Endamoeba histolytica, and 2, Chilomastix).

Ninety-two children were left. None of them showed evidence of tuberculous infection, of syphilis or of any other disease. In their cases no explanation of the symptoms and findings other than infection with Giardia lamblia could be revealed by the most precise clinical and laboratory examinations.

All the symptoms found were compared with those of healthy children of the same age. Besides, a control group of 92 parasite-free children was collected without any selection. It was composed of 42 boys and 50 girls of the same age as the infected children and living under similar conditions.

SYMPTOMS

Some of infected children were symptomless and some had symptoms of no significance. But gastrointestinal complaints, anemia and inadequate development were present in a high percentage of cases.

Aside from the common infectious diseases without complications, the histories showed that 6 children had dysentery and 2 typhoid fever from two to five years before the present examinations.

In the following tabulation the main complaints in the histories of the infected children are compared with those of the control group:

Complaints	92 Infected Subjects	92 Controls
Anorexia	47	15
Headache	49	21
Dizziness	33	7
Abdominal pain	41	..
Blood or pus in the stools	19	4
Irregular bowel movement	57	..

Anorexia, dizziness and abdominal pain were frequent. Anorexia could be recorded for half of the infected children, many of them having, according to the parents, extremely poor appetites. Frequent headache was reported for more than half and dizziness for more than a third of the infected subjects.

Pain in the abdomen was also a frequent complaint, being mentioned by about half of the children who were examined. This symptom, together with the loss of weight and the anemia, was often observed by the parents. In most instances it was localized to the hepatic region; it had a dull, pulling character, started one-half to one hour after eating and lasted one or two hours. Intense, acute pain over the cecal region was no rarity; it was reported that this type of pain was independent of meals and appeared in cramplike attacks. Mucus, pus or blood had been seen in the feces of one fourth of those who were infected. Two thirds complained of irregular bowel movements.

Intestinal Activity	92 Infected Children
Obstipation	11
Obstipation alternating with diarrhea	9
Two stools per day	23
Three stools per day	10
More than 3 stools per day	4
Irregularity of movements	57
One normal stool per day	35

It is unnecessary to state that similar conditions cannot be found in healthy children.

On physical examination it was remarkable to find that 51 of the infected children were asthenic while only 13 were of athletic constitution.

No pathologic condition could be revealed by the physical examination of the lungs, hearts and kidneys of the 92 infected subjects.

A strikingly large number showed sensitiveness on abdominal palpation, pain being elicited in most instances over the duodenal and hepatic

area or over the cecum and the ascending colon. In the 92 children the site of pain is given in the following tabulation:

Site of Abdominal Pain on Palpitation	Number of Cases
Ileocecal region	10
Right upper quadrant	22
Left upper quadrant	3
Entire right side	18
Right and left upper quadrants	4
Right lower and upper and left upper quadrants	1
Entire abdomen	3
Painful on palpation	61
Not painful on palpation	31
	92

Muscular rigidity could be noted, especially in those cases in which the region of the appendix was sensitive, sometimes also in those in which the pains were situated in the right upper quadrant. The defense was characterized by varying intensity. The muscles were constricted and stone hard, but after a few minutes, even if a slight resistance remained, the abdomen became easily palpable. The pains and the character of resistance often showed similarity to those of acute appendicular crisis. Differentiation was sometimes difficult without laboratory tests, but it may be of help to note that (1) the resistance was not constant, (2) the temperature usually did not rise above 37.5 C. (99 F.) and (3) the pains were not localized to a circumscribed point, sometimes extending all over the right side. If on palpation of the descending colon pain was felt on the right side, it was uncertain and dull, as a rule, was of varying appearance and extended over a large area.

The liver was palpable in 36 of the infected children (40 per cent).

In accordance with reports of many authors, no marked changes were found in the number of white blood cells or in the differential count.

Erythrocyte counts and determination of the value of the hemoglobin content were made for 81 of the infected children and for 81 members of the control group. The hemoglobin content was above 80 per cent in only one third of the infected children, being below this figure in two thirds; the lowest values were 40 per cent, 43 per cent and 44 per cent. On the other hand, 72 of the 81 control children showed hemoglobin values over 80 per cent. Corresponding results were given by the erythrocyte counts. Taking 4,000,000 red blood cells per cubic millimeter as the lowest limit of normality, still 52 children of the 81 were anemic. The lowest counts recorded were 1,780,000; 2,080,000, and 2,570,000. In the control group no more than 19 showed values under 4,000,000. More detailed particulars are given in table 2.

The developmental condition of all the infected subjects was established by accurately measuring their heights and weights. The data were

compared with those in the tables of Schlesinger, which give the most appropriate values for conditions in Hungary. For the sake of comparison, the heights and weights, converted into development quotient, were expressed in percentage of the normal development at the respective ages, which was taken as 100 per cent. The advance or retardation of development was also calculated in months.

TABLE 2.—*Hemoglobin Values and Erythrocyte Counts of Eighty-One Infected and Eighty-One Control Children*

	Infected Children		Controls	
	No.	%	No.	%
Hemoglobin, %				
Over 80	26	32	72	89
71-80	23		8	
61-70	21		1	
51-60	6	55-68	..	9-11
41-50	4		..	
Below 40	1		..	
Erythrocyte counts				
Over 4,000,000	29	36	62	77
3,510,000-4,000,000	19		16	
3,010,000-3,500,000	17		3	
2,510,000-3,000,000	12	52-64	..	19-23
2,010,000-2,500,000	3		..	
Below 2,000,000	1		..	

TABLE 3.—*Variation in Development of Ninety-Two Infected and Ninety-Two Control Children Reckoned in Months*

No. of Months	Infected Children		Controls	
Overdeveloped				
16-20	1		6	
11-15	2		11	
6-10	5		20	
1- 5	5		16	
Underdeveloped		Normal		Normal
5- 0	10		24	
10- 6	6		11	
15-11	10		4	
20-16	16		..	
25-21	10		..	
30-26	8		..	
35-31	7		..	
40-36	3		..	
45-41	2		..	
50-46	4		..	
55-51	2		..	
60-56	1		..	

A variation in height of ± 10 per cent from the average of the tables was considered as normal. Thus the height of only 12 infected children was not satisfactory, while none of the controls were below the limit. Development in height was, according to this, only slightly impaired in the infected children.

The most striking difference between the infected and the healthy subjects was shown by the comparison of weights. Of 92 infected children, only 13 attained or surpassed the average weight, while 79 or 86 per cent were below it. Even if a difference of ± 15 per cent is

considered normal, 46 children, just half of those infected, were retarded in development. The discrepancies are easier to perceive when the retardation is calculated in months instead of in percentages (table 3).

Fifty-three children, nearly 60 per cent, were retarded by more than fifteen months' growth, and 12 by more than three years' growth. The minimum values were shown by a girl of 13 who weighed only 24 Kg., which is the average weight of an 8 year old child, and by a boy of 10 who did not attain the 6 year average. On the other hand, nearly 60 per cent of the controls surpassed the average weight, and none of them were under the limit of the fifteen months' deficiency.

According to these figures, the growth of the infected children was not equally retarded, the development of their height being but slightly impeded and that of their weight considerably. The children were strikingly thin.

The hepatic disorders often found in adults were not present in our cases.

Thus far the symptoms have been discussed one by one. The results are summed up in the following tabulation:

Symptoms	Number of Children
Abdominal complaints	9
Anemia	8
Underdevelopment	13
Abdominal complaints and anemia	9
Abdominal complaints and underdevelopment	10
Anemia with underdevelopment	5
Abdominal complaints, anemia and underdevelopment	17
Symptoms found	71
No symptoms found	21
	92

In this compilation the criteria for data on development were further restricted, "underdevelopment" meaning that the weight was more than eighteen months behind the average of the child's age. "Anemia" means a hemoglobin value below 80 per cent together with an erythrocyte count of less than 4,000,000. Even with these limitations no more than about one fourth of the infected children were symptomless, while roughly 75 cent cent showed signs of disease.

RESULTS OF TREATMENT

One cannot be certain whether the registered complaints and symptoms are due to the presence of Giardia unless they decrease or disappear after treatment; that is, unless the cysts disappear from the feces. Many different drugs have been and are used in therapy for giardiasis. The one used in the present study in every instance was acetarsone. Treatment was started with 0.04 to 0.10 Gm. a day according to age, the doses being raised to 0.25 to 0.50 Gm. a day; one course lasted three

weeks. Though giardiasis has been reported to be obstinate and refractory to treatment, this could not be observed in the present cases. Sometimes the cysts disappeared in eight or ten days; with the exception of 3 cases, by the end of the third week tests on all the treated patients gave negative results; that is, cysts could no longer be detected in the stools by examinations following a cathartic of sodium sulfate on three consecutive days. It cannot be stated for certain that the cure will be permanent, but reexamination of the feces of 2 children eight months later and that of 5 children five months later did not reveal cysts.

Thirty-two children were treated. Of these 29 were cured, while 3 still harbored parasites. Particulars about those successfully treated are summarized in table 4.

TABLE 4.—*Effect of Treatment on Twenty-Nine Children*

Findings	Before Treatment	After Treatment
29 children		
Giardia present	29	..
Anorexia	26	3
Headache	17	..
Dizziness	15	3
Irregular bowel movement	18	..
Abdominal pains	21	1
Abdominal pain on palpation	23	1
19 anemic children		
Average value of hemoglobin	57%	89%
Average of erythrocyte counts	3,009,000	4,416,000
20 underdeveloped children		
Average retardation	38 months	11 months
Average monthly gain in weight over normal amount	About 2.4 Kg. or 6 months	

All the complaints ameliorated or vanished after expulsion of the parasites. The appetite improved, in some instances strikingly. The number of bowel movements was reduced to one a day. Abdominal pains and cramps disappeared, and palpation was no longer painful.

Nineteen children were anemic. Before treatment their average values were 57 per cent for hemoglobin content and 3,009,000 for erythrocytes. After treatment the values were 89 per cent and 4,416,000, respectively. Regeneration was fairly quick. In two months the hemoglobin content and erythrocyte count of a patient rose from 44 per cent to 85 per cent and from 2,080,000 to 4,380,000, respectively. In another case the values of 50 per cent and 2,670,000 were changed to 85 per cent and 4,620,000, respectively, in three weeks.

Twenty of the treated children were underdeveloped: that is, more than eighteen months behind the average. The average retardation of their weights was thirty-six months before treatment and eleven months afterward. The average increase in weight amounted to about 2.4 Kg. a month more than the normal development. The weight put on in a month

corresponded to six months' development of a normal child of the same age. A child with a retardation of more than three years' development in four and one-half months acquired normal weight. Three others put on 8, 7.5 and 6.6 Kg., respectively, in two months.

Treatment was not successful in 3 cases. The same drug was administered in the same manner as in the other cases. At reexamination a month later infection still persisted, the complaints and anemia being invariably present. One child weighed the same as before treatment, one 1.5 Kg. less and the third 0.9 Kg. less. These children gave proof that regeneration of those who were cured was due not to the stimulating effect of arsenic but to its antiparasitic effect. Moreover, 11 of the treated children had taken various tonics before treatment without success.

COMMENT

All the symptoms of the observed children may be explained by the impeded resorption capacity of their intestinal tracts. Several series of examinations showed that the circulation of dyes and the resorption of sugar, of proteins and especially of fat were greatly hindered in the infected children, though all their ferment values and digestive processes were perfectly normal. It would lead too far to enumerate the data and proofs here in detail; they will be dealt with in another paper.

According to the findings, the following complaints and symptoms characterize a great number of Giardia-infected children: anorexia, frequent headaches and dizziness, irregular or frequent bowel movement and uncertain pains in the abdomen, usually after meals. The children were anemic and thin; their development in weight being hindered while that in height was normal. Muscular rigidity and pains on abdominal palpation could be observed. The defense was of varying intensity. The pains were felt mostly in the cecal or the hepatoduodenal region; they were not constant or localized to a circumscribed point. The liver was palpable in many instances.

Cases of acute and of chronic involvement were not dealt with separately in the present observations, nor was there a study of the number of cysts excreted. Many authors have declared that they attach a certain importance to the excretion of cysts, stating that symptoms cannot be caused unless the flagellate is present in great numbers in the stools. But in my practice severe symptoms were seen in children in whose feces cysts could be detected only with difficulty, and, on the contrary, several patients passing a large number of cysts were found to be free from symptoms.

The connection of the findings with the infection is shown by the facts that (1) no other cause of disease could possibly be revealed in the children by the most precise examinations and (2) the symptoms dis-

appeared after treatment of the giardiasis. Regeneration of the blood of anemic children and rapid development of those who were retarded in weight quickly started after successful treatment. Healing was not a consequence of the tonic action of arsenic. In 3 cases in which treatment had not been successful the symptoms were further aggravated.

SUMMARY AND CONCLUSIONS

According to the present study, the infection of children with Giardia lamblia is symptomless or causes insignificant complaints in only one fourth of the cases. This means that the proportion of carriers who are healthy is only a third of that generally assumed. In the majority of cases infection is followed by an acute disease which may become chronic, leading to anemia and abdominal complaints and impeding the normal development.

TREATMENT OF GONOCOCCIC INFECTIONS IN CHILDREN WITH SULFANILAMIDE

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On the suggestion that the gonococcus was one of the organisms susceptible to sulfanilamide, it was decided to treat gonorrheal vaginitis in children by oral administration of sulfanilamide in further search for a simple and effective method of handling this therapeutic problem. After encouraging results had been obtained in cases of vaginitis, sulfanilamide was applied to the treatment of gonorrheal urethritis in boys and of gonorrheal conjunctivitis.

This report summarizes the results of treatment with sulfanilamide in 9 cases of conjunctivitis, in 5 cases of urethritis in boys and in 22 cases of vaginitis in girls since May 1937.

Diagnosis of gonococcic infection was made on the basis of the finding of gram-negative intracellular diplococci, morphologically typical of gonococci, in smears from the eyes, urethra or vagina. Gonococcic complement fixation tests made on admission were positive in about two thirds of the patients. Cultures for gonococci were not available to confirm the diagnosis.

Since bacteriologic examination is the accepted criterion of cure of gonococcic infection, the use of daily vaginal, urethral or conjunctival smears provided an objective laboratory method of following the response to sulfanilamide therapy. Clinical improvement, considered on the basis of subsidence of visible inflammatory reaction and cessation of discharge, was correlated with the laboratory reports in evaluation of the results of treatment.

The dose of sulfanilamide which was used was calculated on the recommendation of Long and Bliss,[1] giving 1 Gm. per 20 pounds (9.1 Kg.) of body weight, daily, taken in three or four doses at equal intervals throughout the twenty-four hours. The first few patients received doses relatively much smaller, a fact which, it is thought, was responsible for the failure in these cases. A few patients received larger doses without showing any evidence of toxicity. The dose is decreased after a favor-

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1. Long, P. H., and Bliss, E. A.: Para-Aminobenzenesulfonamide and Its Derivatives, J. A. M. A. **108**:32 (Jan. 2) 1937.

able response is noted, but medication is continued for seven to ten days. To patients who showed no response the full dose was given for a period of two weeks in order to insure an adequate trial of the drug. Gastrointestinal symptoms in infants and the development of fever and a rash

TABLE 1.—*Gonococcic Conjunctivitis Treated with Sulfanilamide*

Age in Yrs.	Weight in Pounds	Complications	Gonococcic Complement Fixation Test	Unfavorable Reaction	Time in Days for Negative Smears to Be Obtained	Time in Days Till Clinical Improvement Was Noted	Daily Dose in Gm.	Duration of Treatment in Days
8	77	Vaginitis; corneal ulcer	Negative	None	3*	3	3.0 2.0 1.0	2 9 2
3	30	Urethritis	Negative	None	8*	4	2.6	8
4	34	Vaginitis; corneal ulcer	Positive	None	2	4	2.6 2.0 1.3	3 5 4
Newborn	2½	Prematurity	Not done	Loose stools	1	1	0.13	3
Newborn	5	Prematurity	Doubtful	None	1	½	0.2	3
Newborn	8½	None	Doubtful	Vomiting; loose stools	4*	½	0.3	4
Newborn	5½	Prematurity	Positive	Loose stools	1	½	0.26	2
6	..	None	Negative	None	1	½	1.3 0.6	4 3
Newborn	7½	None	Negative	None	No response		0.3	33

* First smear done after institution of treatment.

TABLE 2.—*Gonococcic Urethritis Treated with Sulfanilamide*

Age in Yrs.	Weight in Pounds	Complications	Gonococcic Complement Fixation Test	Unfavorable Reaction	Time in Days for Negative Smears to Be Obtained	Time in Days Till Clinical Improvement Was Noted	Daily Dose in Gm.	Duration of Treatment in Days
3	30	Conjunctivitis	Negative	None	7*	..	2.6	8
6	..	None	Positive	Rash; fever	4*	2	2.6	8
3	27	Prostatitis; chronicity	Positive	None	5*	..	0.6 1.0	2 26
6	40	None	Positive	None	1	1	2.6	3
4	42	Meatotomy	Positive	None	No response (concentration in blood 22.7, 9.75, 9.6 mg. per 100 cc.)		2.0 2.6	13 21

* First smear done after institution of treatment.

were considered sufficient reason for discontinuing treatment. Transfer to another hospital because of an intercurrent contagious disease interrupted treatment in a few cases, so that several patients received less than the desired amount of treatment. (For details of treatment, see tables.)

Nine patients with conjunctivitis were treated with sulfanilamide by mouth and received local treatment, in the form of boric acid irrigations, only as often as was necessary to keep the eyes clear of pus. Three of these patients were given a period of local treatment alone, consisting of a 10 per cent solution of mild protein silver or metaphen 1 : 4,000 and of frequent irrigations (as often as every half-hour), for three to ten

TABLE 3.—*Gonococcic Vaginitis Successfully Treated with Sulfanilamide*

Age in Yrs.	Weight in Pounds	Complications	Gonococcic Complement Fixation Test	Unfavorable Reaction	Time in Days for Negative Smears to Be Obtained	Time in Days Till Clinical Improvement Was Noted	Daily Dose in Gm.	Duration of Treatment in Days	Duration of Follow-Up in Months
7	40	Str. haemolyticus septicemia	Not done	None	2	2	2.6 1.3	7 7	8
5	36	None	Positive	None	7	5	2.6	7	8½
8	77	Conjunctivitis	Negative	None	1	3	3.0 **2.0** 1.0	2 9 3	7
8	43	None	Positive	Rash; fever	1	..	3.0 2.0	2 9	7
7	50	None	Doubtful	None	2	..	2.6 1.3	9 and 9 4 and 3	2½
4	36	Conjunctivitis	Positive	None	2	..	2.6 **2.0** 1.0	2 5 5	1½
5	34	None	Negative	None	1	2	2.0 1.0	3 7	5½
2	29	None	Positive	None	2	..	1.3	13	3
4	34	None	Positive	None	1	1	2.6 **1.3**	6 **10**	4
10	52	None	Positive	Rash	1	2	3.0	10	3
4	30	None	Doubtful	None	1	..	1.3 0.6	7 7	5
1	24	None	Positive	None	1	2	1.0	5	2
2	26	Salpingitis	Positive	None	2	4	1.3 0.6	7 5	2½
2	1st 24	None	Negative	None	No response		1.3	14	
	2d 25	None	Negative	None	2	2	1.3 0.6	3 10	2
9½	1st 57	None	Positive	None	No response		2.6	14	
	2d 64	None	Positive	Nausea	2	2	3.3 2.6	7 10	2
6	1st 47	None	Positive	None	No response		2.6	14	
	2d 47	? reinfection	Positive	None	2	..	2.6 1.3	6 6	4

days without any evident improvement. Corneal ulceration was present in only 2 cases and probably had occurred before treatment was instituted, although because of periocular edema and chemosis it was not observed until after treatment with sulfanilamide had reduced the inflammatory reaction. Eight of the 9 patients responded promptly to sulfanilamide therapy, so that irrigations were required only at two or three hour intervals after one or two doses of the drug, and within a very few days could be discontinued. The one patient given treatment who did

not respond showed clinical improvement, having only scant discharge, but for thirty-three days continued to show positive smears throughout treatment with adequate doses. For the other patients negative smears were obtained after an average of two and a half days.

This method of treating gonococcic conjunctivitis decreased the duration of the disease and the period of hospitalization required in these cases. It proved especially valuable in diminishing the frequency of irrigations, which are so detrimental to newborn and premature infants and so exhausting to older children. The results of this series add further evidence to the report of Willis [2] that in cases of gonorrheal conjunctivitis, sulfanilamide gives a more rapid cure than any other method of treatment.

In 4 of 5 cases of urethritis in boys, 3 to 6 years of age, there was prompt response to treatment with sulfanilamide. One was a boy

TABLE 4.—*Gonococcic Vaginitis Treated Unsuccessfully with Sulfanilamide*

Age in Yr.	Weight in Pounds	Complications	Gonococcic Complement Fixation Test	Unfavorable Reaction	Smears	Clinical Improvement	Daily Dose in Gm.	Duration of Treatment in Days
2	25	Arthritis	Positive	Fever; rash; drowsiness	No response	None	1.3	22
1½	26	None	Negative	None	No response	None	1.3	15
4	28½	Salpingitis	Positive	None	No response (concentration in blood 12.6, 25.0 mg. per 100 cc.)	None	1.4 2.0	7 13
7	50	Salpingitis	Positive	None	No response	None	1.0	12
8	60	Salpingitis	Positive	None	No response	None	1.0	7
11	73	Salpingitis	Positive	None	No response	None	2.6	16

with chronic prostatitis who had not responded to prolonged local treatment or to the use of Corbus-Ferry filtrate. The others were patients with acute infection and received no other treatment except sitz baths and meatotomy when necessary. One patient continued to have positive smears throughout treatment with sulfanilamide for a period of thirty-four days, although the discharge became very slight. The concentration of sulfanilamide in the blood during this period ranged from 9.6 mg. to 22.7 mg. of free sulfanilamide per hundred cubic centimeters of blood, figures which suggest that some factor other than the dose or absorption of the drug was responsible for this failure. In the other 4 cases, negative smears were obtained after an average of four days, coinciding with the cessation of discharge (table 2).

Gonorrheal vaginitis was treated with sulfanilamide orally in 22 children. All of these had acute infection with profuse discharge and

2. Willis, T.: Sulfanilamide in Ophthalmia Neonatorum, Yale J. Biol. & Med. **10**:275 (Jan.) 1938.

typical positive smears. Therefore, the response to treatment was definite, both in diminution of discharge and in change of the character of the smear. No other treatment was used except external cleanliness and, for those who had some complication, symptomatic treatment. In this group were 5 patients who had abdominal signs and symptoms sufficient to be considered evidence of tubal or peritoneal involvement. One child had arthritis involving the small joints of the foot; 2 had gonorrheal conjunctivitis, and 1 had Streptococcus haemolyticus septicemia with various complications. The arthritis, conjunctivitis and septicemia were all favorably influenced by sulfanilamide therapy. In the cases in which there was suspicion of salpingitis, it was impossible to say that the course was altered by this treatment, as in other cases in which treatment was palliative the condition has subsided just as well.

Thirteen patients showed a prompt and definite response to sulfanilamide therapy, with cessation of discharge and with consistently negative smears after an average of two days of treatment. The cases of 3 other patients are notable in that the infection failed to respond to an adequate trial with sulfanilamide and was subsequently cleared up by treatment with estrogen, only to recur within a short time; then, when a second trial of sulfanilamide was made, the disease responded satisfactorily within forty-eight hours. These make a total of 16 patients, or more than two thirds of the series, who have been successfully treated with sulfanilamide. In 3 of the cases of failure, an inadequate dose of the drug seems to be accountable for the failure to respond. In 1 of the other cases in which there was no response, studies of the concentration in the blood showed a consistently high level of free sulfanilamide, ranging from 12.6 mg. to 25 mg. per hundred cubic centimeters, suggesting again that dosage and the concentration in the blood are not the only factors which determine the response to this drug.

There have been no serious reactions to sulfanilamide in this group of 33 patients. There were mild reactions attributable to the drug in 7 cases. Gastrointestinal symptoms, consisting of loose stools, nausea and vomiting, occurred in 3 babies and in 1 older child. Although these were mild in all cases, the potential seriousness of diarrhea in small infants was considered an indication for discontinuing treatment in the 3 infants. A rash occurred in 4 children, accompanied by a moderate elevation of temperature in 3 of them. The rash, similar in all cases, was so suggestive of measles that the first child to show it was transferred to an isolation hospital. Because of the rapid disappearance of the rash and the lack of constitutional symptoms, the diagnosis of measles was questioned, and when a single dose of sulfanilamide reproduced the rash and the febrile reaction, there was no doubt as to the cause. In another child, a repetition of the rash and elevation of temperature resulted from a single dose given after the first reaction had subsided,

showing the relation of those symptoms to the drug. One patient had a fall of 15 per cent in hemoglobin accompanying the rash. No other changes in the blood were observed. No unfavorable reactions occurred in those receiving prolonged treatment or in those who were given a second course of treatment. However, because of the possible serious reactions to this drug, it is considered very important that patients be closely observed during treatment with sulfanilamide, preferably in the hospital, with frequent complete blood counts.

There have been no recurrences of symptoms or positive smears during the follow-up period, ranging from one to eight months.[3] Although the series is small and the interval relatively short, this record presents a decided contrast to that of treatment with other methods in the clinic of the Bellevue Hospital which show recurrences in about a third of the cases. A possible explanation of this may be that sulfanilamide in the circulating blood reaches the gonococci in all tissues, thus clearing all foci for possible reinfection which are inaccessible to other methods of treatment.

SUMMARY

Sulfanilamide administered orally has been successful in treating gonococcic infections in children in 8 of 9 cases of conjunctivitis, in 4 of 5 cases of urethritis, and in 16 of 22 cases of vaginitis.

This method of treatment has greatly lessened the duration of the disease and the necessity for local treatment.

Daily doses of 1 Gm. per 20 pounds (9.1 Kg.) have been found to be effective and without unfavorable reaction in a large percentage of cases in the series.

No recurrences have developed during the follow-up period.

The factors responsible for failure to respond to sulfanilamide therapy remain to be determined.

3. Since the writing of this report, continued follow-up with monthly examination and smears has shown that 10 patients have remained well over a period of ten to fourteen months, 3 for seven to eight months and 3 for one and one-half to three months.

EVIDENCES OF DISTURBED PRENATAL AND NEONATAL GROWTH IN BONES OF INFANTS AGED ONE MONTH

II. CONTRIBUTING FACTORS

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In a previous communication, one of us [1] has described the appearance and incidence of circular striae in the tarsal bones of infants at the age of 1 month. These striae appeared in lateral roentgenograms of the foot as fine white lines, usually from 0.5 to 1 mm. inside the margin of the calcaneous and of the talus. In a few instances there were present about the periphery solid bands or thickened temporary zones of calcification which later became resolved into a stria. We have interpreted these annular striae and thickened temporary zones, shown diagrammatically in the figure, as representing the same kind of physiologic process as do the striae caused by growth in long bones. Eliot, Souther and Park,[2] Kohler,[3] Sontag and Comstock [4] and others have described such striae of the long bones. There is evidence that they may be produced by any factor which sufficiently retards or stops osseous growth. They are frequently seen following severe illness or a surgical operation. Striae of the long bones also appear as a result of disturbed mineral metabolism and therefore are frequently seen after healing in rickets. In this instance, the mechanism may be different from that by which striae are formed during retardation in growth, but the appearance of the striae is the same.

The annular striae described in our first communication were found in the tarsal bones of 63 per cent of 98 infants at the age of 1 month. They were apparently laid down at or immediately after birth. The

The authors wish to acknowledge the assistance rendered by Mr. Robert Eastman in the preparation of tables and figures included in this paper.

1. Sontag, L. W.: Evidences of Disturbed Prenatal and Neonatal Growth in Bones of Infants at One Month, Am. J. Dis. Child. **55**:1248 (June) 1938.

2. Eliot, M. M.; Souther, S. P., and Park, E. A.: Transverse Lines in X-Ray Plates of the Long Bones of Children, Bull. Johns Hopkins Hosp. **41**:364-388 (Dec.) 1927.

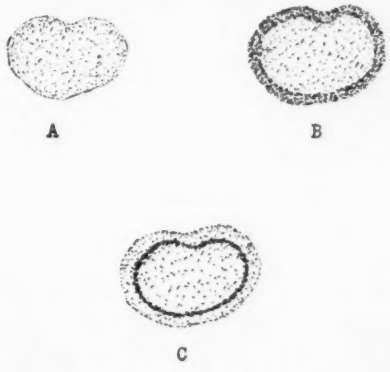
3. Kohler, A.: Roentgenology, New York, William Wood & Company, 1928.

4. Sontag, L. W., and Comstock, G.: Striae in the Bones of a Set of Monozygotic Triplets, Am. J. Dis. Child. **56**:301 (Aug.) 1938.

reasons for this conclusion are that these striae were never present in roentgenograms taken at birth and that superimposition of roentgenograms taken at 1 month on those of the same child which were taken at birth showed that the outlines of the striae, when they were present, exactly coincided with the periphery of the bones at birth.

The object of this paper is to present data on the pregnancies, the nature of the birth and the progress after birth of the 98 children whose roentgenograms were studied, in order to clarify, if possible, the etiology of the striae.

It seems to us that the shock of birth itself is the factor most likely to produce a retardation in growth or a cessation of sufficient degree to cause these striae. The marked striae in the long bones resulting from interruptions in growth incident to surgical procedures in



These three diagrammatic drawings of roentgenograms represent, *A*, a lateral view of a normal tarsal bone at birth; *B*, a similar view, at the age of 1 month, showing a dense band or temporary zone of calcification about the bone, and *C*, a view at 1 month showing a stria or fine white line just inside the margin.

young children lend weight to the belief. If our theory is correct, those births which were severe and difficult from the standpoint of the infant would be the most likely to produce striae. An examination of data on the nature and the severity of the delivery as they affect the child would help us to substantiate or to deny the significance of natal shock as an etiologic factor in the production of striae of the tarsal bones.

Obviously, however, data on the length of labor, the use of forceps, etc., are not entirely satisfactory for our purpose because they do not show the actual degree of shock suffered by a child at birth. A forceps delivery may in some instances be accomplished with no more shock than the average spontaneous delivery. On the other hand, the incidence of severe shock to the fetus is undoubtedly larger in a series of forceps deliveries than in the average series of spontaneous ones. Sim-

ilarly, precipitous labor may be the result of severe uterine contractions which cause rapid molding of the head with almost continuous pressure; on the other hand, it may be the result of a large pelvis, relaxed perineal muscles and a small child. In the latter event, the likelihood of severe shock would be slight. Here again, however, one would expect to find that the incidence of shock to fetuses in a series of precipitate labors would be greater than in a series of spontaneous labors of normal length. The difficulty in establishing respiration might offer a criterion for shock in a few instances, but in our series of cases, in which the babies were delivered by some twenty physicians of widely different training and experience, what one physician considers difficulty in establishing respiration may not be so to another. Records of labor are therefore not comparable enough in this respect for a decision on the difficulty of establishing respiration.

Since the severity and effect of the shock of the natal process, like the shock of a direct surgical process, should depend not only on the operation itself but on the condition of the infant, we have studied some of the factors during gestation which might conceivably influence the condition of the fetus and its ability to withstand the process of birth. The maternal factors we have considered, namely, the mother's metabolism, nutrition, hemoglobin levels and health, are such that they might also affect the infant's mineral metabolism, though hardly to the extent of producing fetal rickets. Such maternal factors as have been mentioned are no more clearcut or free from difficulty of interpretation than are the labors. If, for instance, a woman suffering from persistent vomiting during most of her pregnancy has had her stores of mineral and nitrogen depleted by an immediately previous pregnancy, the effect on the fetus might be much greater than had she been in good condition at the time of conception.

Because the nature of the early feedings of the infant might conceivably be a factor, we have considered the matter of breast feeding and of the child's gain in weight during the first month. For all of the factors which we have considered, we have presented the incidence among the group showing striae as compared with the incidence in the group not showing striae. A comparison of the data in the two groups is shown in tables 1 and 2.

From table 1 it is evident that the incidence of difficult delivery, as indicated by the use of forceps, was much greater (31 per cent) in the group showing striae than in the group showing no striae (6 per cent). The incidence of precipitate delivery, which was arbitrarily defined as involving less than six hours of total labor, was also much greater in the group with striae, being 31 per cent in this group and 15 per cent in the other. Thirty-nine per cent of those children showing striae were first born, whereas only 19 per cent of the others were first born. The

incidence of labors longer than eighteen hours is not appreciably different in the two groups. The weight of the infants in the group with striae is approximately the same as in the group without striae, being 7.63 ± 0.13 pounds (3,466 ± 61.2 gm.) for the former and 7.7 ± 0.17 pounds (3,543 ± 75.7 gm.) for the latter. There is no indication from these figures that either the size of the child, as it might contribute to a more difficult birth, or maturity, as it might influence the ability of the fetus to withstand shock, is a factor.

TABLE 1.—*Comparison of Factors of Gestation and Birth for Mothers of Infants With Striae and Those of Infants Without Striae*

Factor	Percentage of Incidence in Mothers of Infants With Striae	Percentage of Incidence in Mothers of Infants Without Striae
Forceps delivery	31	6
Precipitate delivery	31	15
Primiparity	39	19
Long labor	8	9
Basal metabolic rate below 0%	26	19
Persistent nausea and vomiting	25	8
Poor health	6	0
Hemoglobin control below 70%	42	36
Inadequate economic status	10	0

TABLE 2.—*Comparison of Infants' Weights and of Maternal Weights, Basal Metabolic Rates and Hemoglobin Values for the Group With and the Group Without Striae*

	Mean Values for Group With Striae	Mean Values for Group Without Striae
Weight of mothers (nonpregnant)	131.80 ± 2.67 lb.	123.40 ± 1.68 lb.
Basal metabolic rate of mothers (ninth month)	+7.58 ± 1.58%	+6.70 ± 1.49%
Serum calcium of mothers (ninth month)	10.560 ± 0.137 mg. per 100 cc.	10.060 ± 0.160 mg. per 100 cc.
Weight of infants	7.63 ± 0.13 lb. (3,466.0 ± 61.2 Gm.)	7.70 ± 0.17 lb. (3,543.0 ± 75.7 Gm.)
Weight gain of infants	1.350 ± 0.108 lb. (600.0 ± 48.7 Gm.)	1.147 ± 0.141 lb. (529.0 ± 64.0 Gm.)

Next to be considered are those factors which might conceivably influence the ability of the infant to resist the shock of birth. While there are doubtless many of these, only a few lend themselves to measurement or satisfactory estimation.

One of the factors which may interfere with the mother's nutrition during pregnancy and therefore possibly with the nutrition of the fetus is persistent vomiting or persistent nausea of sufficient intensity to limit food intake. It is difficult to define that degree of nausea and vomiting likely to produce significant nutritional deficiencies. It is in fact difficult to define any given degree of nausea. We have therefore had to be arbitrary in our definition. We have considered nausea and vomiting

persistent when the nausea occurred daily, with vomiting one or more times per week for twenty weeks after the estimated date of conception. On this basis, 25 per cent of those children showing striae were born of mothers who suffered from persistent nausea and vomiting, while only 8 per cent of those without striae were born of such mothers.

We have compared weights of mothers of infants with and without striae during periods when they were not pregnant because we felt that excessive weight might be evidence of a higher incidence of metabolic or endocrine disturbance. The average weight of mothers of the infants with striae when they were not pregnant was 131.8 ± 2.67 pounds (59.8 ± 1.2 Kg.) as compared with 123.4 ± 1.68 pounds (56 ± 0.8 Kg.) for the other mothers. The difference in weight existed in spite of the fact that there was a much higher percentage of primiparas in the former group, which fact would lead us to expect a lower average weight. We believe that it is significant. This difference of 8.4 pounds (3.8 Kg.) between the weight of the mothers of the infants with striae and the weight of the mothers of infants without striae dropped to 5.4 pounds (2.4 Kg.) at the end of pregnancy. This decrease in the difference between the two groups of mothers from conception to term was consistent with the higher incidence of persistent nausea and vomiting in the mothers of the striated infants. Such a condition, when severe, should inhibit a large gain in weight. Actually, many of the mothers with persistent nausea and vomiting lost considerable weight during the first six months of pregnancy, and some were barely able to regain the weight of the nonpregnant period by the ninth lunar month.

While there was what appeared to be a significant difference in weight between the two groups of mothers when they were not pregnant, a comparison of their basal metabolic rates at the ninth month shows no significant difference. The figures are 7.58 ± 1.58 per cent for the mothers of the infants with striae and 6.7 ± 1.49 per cent for those of the infants without the striae. There was a slightly greater incidence of ratings below 0 per cent at the ninth month in the mothers of the group with striae.

We have considered the anemia of pregnancy, again because we felt that if severe enough it might affect the well-being of the fetus. Unfortunately, information on the hemoglobin content was available in most instances only at the sixth and at the ninth month and not in the interval between, when it would be likely to be lowest. We have arbitrarily divided our mothers into two classes, in one of which the hemoglobin content was 70 per cent or above at the ninth calendar month and in the other, below that figure. The slight difference in the incidence of readings below 70 per cent between the mothers of the

infants with striae and those of the infants without striae is probably not significant.

Another factor considered was the calcium content of the maternal serum, which was not appreciably different for the two groups, being 10.55 ± 0.137 mg. per hundred cubic centimeters for the mothers of the infants with striae and 10.5 ± 0.16 mg. for those of the infants without striae at the ninth month.

The incidence of poor health of the mothers is low, if the persistence of nausea and vomiting is excluded. While it may therefore have been an important factor in the production of striae in the cases in which it existed, it could not be a factor in most cases. Of the mothers of the infants with striae, 1 suffered from a severe toxic goiter and 1 had persistent pyelonephritis with about 2 degrees of fever throughout almost the whole of pregnancy. One had active pulmonary tuberculosis and weighed 89 pounds (40.4 Kg.) at delivery, and in 1 severe preeclamptic toxemia developed during the last month of pregnancy. There were no such instances of poor health among the mothers of the infants without striae. Six of the mothers of infants with striae were in severely straitened financial circumstances throughout pregnancy, in each instance the entire family having an income of less than $1 per day. No poverty of a comparable degree existed among the mothers of the infants without striae.

The gains in weight of the infants with and without striae are not significantly different, being 600 ± 48.7 Gm. for the former group and 529 ± 64 Gm. for the latter. More than 85 per cent of the infants in both groups were breast fed; therefore, this factor cannot be regarded as important in the production of striae. Of the 6 infants born from ten days to four weeks prematurely, 2 showed striae and 4 showed none. In 3 cases a cesarean section was done. Two of the infants showed no striae, while 1 showed faint striae.

As indicated in our earlier description of these striae, they varied greatly in their clarity and intensity. Their existence did not seem to be a simple "all or none" affair. It is our belief, although we have not substantiated it, that some change in growth occurs in the tarsal bones of all infants after birth, although not all are severe enough to be detected in roentgenograms. In our series the striae ranged from well defined and prominent lines which remained visible on roentgen examination up to the age of 4 or 5 months in some cases to poorly defined fragments of line which disappeared by the third month in other cases. In general, those infants with the more prominent lines had also histories of less normal pregnancies. We shall briefly present here the pertinent data of the pregnancies of the 3 infants in our group rated as having the most pronounced striae.

REPORT OF CASES

CASE 1.—This mother, aged 31, was pregnant for the third time, her last pregnancy having occurred eight years previously. Her pelvic measurements were normal. At conception her weight was 155 pounds (70.3 Kg.); at the ninth lunar month the weight had dropped to 154 pounds (69.9 Kg.), and at the end of the tenth lunar month it was 162 pounds (73.5 Kg.). At the ninth month the basal metabolic rate was + 23 per cent, the calcium content of the serum at the same time being 10.9 mg. per hundred cubic centimeters and the hemoglobin content 73 per cent (Dare). This patient suffered nausea and vomiting through the first six lunar months of gestation. A suicide in the family during the pregnancy produced a rather profound emotional upset and undoubtedly contributed to the feeling of depression which existed throughout much of the gestation. The economic status of the family was rather low but not desperate. Labor lasted eight and a half hours and was dry. The position was not recorded. A low forceps was applied. The attending physician noted no evidence of injury at birth. The infant weighed 8 pounds and 8 ounces (3,856 Gm.) at birth, and the gain in weight during the first month was better than normal. The child was breast fed.

CASE 2.—The mother in this case was a primipara of 19 years with a normal pelvis. Throughout the first seven and a half lunar months she suffered nausea and vomiting. At the ninth month the red blood cells numbered 3,000,000 per cubic millimeter, and the hemoglobin content was 60 per cent (Newcomer). The calcium content of the serum at the same time was 11.3 mg. per hundred cubic centimeters. The weight and the gain in weight were not recorded. At the seventh month the basal metabolic rate was + 22 per cent. It was reported that labor was rather severe and lasted nineteen and a half hours. The position was left occipito-anterior, and the infant weighed 7 pounds and 8 ounces (3,402 Gm.) at birth. The child was breast fed. The gain in weight at the end of one month was 28 ounces (793 Gm.).

CASE 3.—The age of the mother in this case was 22 years. Her weight when she was not pregnant was 120 pounds (54.4 Kg.), and at the end of the seventh lunar month it was the same. The quality of the food available was extremely poor throughout pregnancy, with no milk in the diet. The patient lived with her husband's family and was constantly depressed and concerned over this fact. Throughout the first nine lunar months, nausea and vomiting persisted. The hemoglobin content at the eighth month was 54 per cent (Newcomer). Labor was severe, lasting thirteen and one-half hours. A forceps was applied "to slow the delivery," according to the attending physician. The child, a girl, weighed 10 pounds (4,536 Gm.) at birth. She was breast fed. Although her weight at the age of 1 month is not available, the gain in weight at 2 months was excellent.

SUMMARY

We have compared the characteristics of pregnancies and deliveries of mothers whose infants showed what one of us has previously described as tarsal striae found in roentgenograms taken at the age of 1 month. The progress of these infants from birth to 1 month was also compared. The pregnancies of the mothers of the infants with and without striae differed appreciably in the following respects:

1. The incidence of persistent nausea and vomiting was much greater in the mothers of the infants with striae.

2. All mothers in poor health, other than that occasioned by persistent nausea and vomiting, gave birth to infants in whom striae developed.

3. In the infants of these mothers whose economic status was unusually low striae developed.

4. The mothers of the infants with striae had an appreciably higher weight when not pregnant than did the mothers of the infants without striae.

Deliveries of the infants with and without striae differed as follows:

1. A greater proportion of the infants with striae were first born.

2. The incidence of forceps delivery was much greater among the infants with striae.

3. A greater percentage of the infants with striae were born of precipitate labor.

Other factors, such as the mother's basal metabolic rate, calcium content of the serum and hemoglobin content, the length of labor, the weight of the infant at birth and the gain in weight from birth to the age of 1 month, were not appreciably different for the two groups.

CONCLUSIONS

Our findings lead us to believe that the tarsal striae frequently found in the roentgenograms of 1 month old children are the result of disturbances in growth produced by the process of birth itself and influenced by such factors as maternal health and nutrition. We believe that the shock of birth is an important factor and that it is determined by the severity of the birth process plus the physical condition of the infant. We consider the mechanism comparable to that involved when striae are laid down in long bones of growing children as a result of a surgical procedure or of severe illness.

SULFANILAMIDE ERUPTION

A STUDY OF PATIENTS WITH THE MORBILLIFORM RASH AND OF THEIR SUBSEQUENT REACTIONS

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Sulfanilamide (para-aminobenzenesulfonamide base) and its related compounds have assumed a prominent position in the medical armamentarium during the past two years. Providing as they do a specific and apparently effective form of treatment for a group of conditions previously difficult of therapeutic approach, it is small wonder that the drugs have gripped the medical and the popular imagination. In the face of the widespread and occasionally injudicious use of these drugs, it is surprising how small an amount of experimental work was performed to determine the toxic reactions to them and their therapeutic efficacy before they were launched for clinical trial. It is still to be hoped that such late complications as the cataract due to dinitrophenol will not be the lot of patients benefited by treatment with sulfanilamide.

An increasing number of papers have recently been devoted to the side effects of sulfanilamide therapy. No mention will be made here of the untoward reactions not involving cutaneous manifestations or some change in the leukocytic response. A mere enumeration of the reactions attributed to the sulfanilamide group of drugs would involve several hundred references and would be outmoded before the date of publication.

Domagk [1] in his original article pointed out that previous antistreptococcic agents were too toxic in therapeutic doses. Gold compounds, for example, "cause skin eruptions and damage to the kidneys" which even if they disappear relatively rapidly after discontinuance of the drug reappear immediately with resumption of therapy. To Domagk's knowl-

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1. Domagk, G.: Ein Beitrag zur Chemotherapie der bakteriellen Infektionen, Deutsche med. Wchnschr. **61**:250, 1935.

edge such reactions did not occur with prontosil.[2] Indeed a whole series of the early clinical reports following on the heels of Domagk's paper made no mention of any possible cutaneous manifestations. Typical of the remarks on toxicity is the following statement: "The preparation has been harmless, free from undesired side effects, easily absorbed and effective." [3]

Meyer-Heine and Huguenin [4] were the first to mention the possibility of cutaneous reactions. In reporting on a series of 150 patients with erysipelas who were treated with prontosil, they recorded a single instance of scarlatiniform erythema, which disappeared despite continuation of treatment; this did not refer to the pigmentation of the skin due to the drug itself. Ehlers [5] was the earliest in the German literature to remark on the occurrence of a "drug eruption following large doses" of prontosil. Thereafter almost every report on a series of patients treated with one of the sulfanilamide group mentioned the occurrence of 1 or more examples of cutaneous eruption. To choose an example at random, Unshelm [6] reported in detail 2 cases of eruptions in children with infection of the urinary tract.

The year 1937 saw the adoption of sulfanilamide therapy into general use in the United States. Since then reports of toxic reactions have been forthcoming in ever increasing numbers. Schwentker and Gelman [7] presented an objective description of the so-called sulfanilamide rash. They detailed the appearance, between three and seventeen days after commencement of therapy, of a morbilliform eruption, which occasionally followed several hours of fever and malaise. This eruption faded completely in forty-eight hours if administration of sulfanilamide was stopped but lasted up to seventy-two hours if it was continued. They further reported the occurrence in 1 case of a scarlatiniform eruption which followed subsequent administration. They found no significant

2. The following terminology will be employed: "Prontosil" refers to the original drug, the hydrochloride of 4-sulfamido-2′,4′-diaminoazobenzene. (The "prontosil" known as a proprietary preparation in the United States, and now to be called "neoprontosil," is the old "prontosil soluble," the disodium salt of 4-sulfamidophenyl-2′-azo-7′-acetylamino-1′-hydroxynaphthalene-3′6′-disulfonic acid.) When "rubiazol" has been mentioned in references from the French literature, we have substituted "prontosil."

3. Klee, P., and Römer, H.: Prontosil bei Streptokokkenerkrankungen, Deutsche med. Wchnschr. **61**:253, 1935.

4. Meyer-Heine, A., and Huguenin, P.: Traitement de l'érysipèle par le chlorhydrate de sulfamido-chrysoïdine, Presse méd. **44**:454, 1936.

5. Ehlers, R.: Die Wirksamkeit des Prontosil in der Go-Behandlung, Med. Welt **10**:1559, 1936.

6. Unshelm, E.: Zur Behandlung von Kindern mit Prontosil, Arch. f. Kinderh. **110**:76, 1937.

7. Schwentker, F. F., and Gelman, S.: Sulfanilamide Rash, Bull. Johns Hopkins Hosp. **61**:136, 1937.

alteration in the leukocytic picture. Although Hageman and Blake [8] emphasized the specific febrile reaction to sulfanilamide, they described the appearance of a morbilliform eruption in 9 cases. In addition, definite hemorrhagic lesions and urticaria-like wheals were noted. During the period of the eruption, the total leukocyte counts were found to vary between 7,000 and 48,000, the polymorphonuclear neutrophils ranging from 63 to 95 per cent. Eosinophils were present in half the cases, numbering from 1 to 6 per cent. Goodman and Levy's cases [9] are worthy of citation because one of the rashes described had a hemorrhagic element. In this case a single dose of sulfanilamide three weeks later produced an erythematous blush of the face and arms with burning and itching, the condition clearing in about twelve hours. No blood counts were recorded. The consensus concerning the leukocytic picture during the sulfanilamide rash has favored either no change at all or polymorphonuclear leukocytosis.

Coincident with increasing interest in the eruptions caused by the drug, greater attention has been paid to changes in the leukocytes in patients during sulfanilamide therapy. This consideration has come to the fore because of the reports of deaths from agranulocytosis supposedly secondary to therapy with the sulfanilamide group of drugs. Although the role played by the medication is doubtful in several of the reported cases, the development of granulocytopenia should not come as a surprise in view of the presence of the benzene ring in the sulfanilamide molecule. On the contrary, the relative infrequency of such cases must be considered fortunate. Indeed, in several large series granulocytopenia has not been mentioned at all. For example, Hageman and Blake,[10] in a complete review of their experience with the drugs, stated that granulocytopenia was not found in any of more than 100 cases. Bigler, Clifton and Werner,[11] however, demonstrated a rapid disappearance of leukocytosis and a tendency to leukopenia in patients who were receiving sulfanilamide. In most of their cases medication was not continued long enough for the fever or rash due to the drug to develop. In the 2 cases presented in detail in which a significant drop in the relative percentage of polymorphonuclear leukocytes occurred, the sulfanilamide had been given for only three days

8. Hageman, P. O., and Blake, F. G.: A Specific Febrile Reaction to Sulfanilamide: Drug Fever, J. A. M. A. **109**:642 (Aug. 28) 1937.

9. Goodman, M. H., and Levy, C. S.: The Development of a Cutaneous Eruption (Toxicodermatosis) During the Administration of Sulfanilamide: Report of Two Cases, J. A. M. A. **109**:1009 (Sept. 25) 1937.

10. Hageman, P. O., and Blake, F. G.: Clinical Experience with Sulfanilamide in the Treatment of Beta Hemolytic Streptococcic Infections, Am. J. M. Sc. **195**: 163, 1938.

11. Bigler, J. A.; Clifton, W. M., and Werner, M.: The Leukocyte Response to Sulfanilamide Therapy, J. A. M. A. **110**:343 (Jan. 29) 1938.

and had been discontinued three and twelve days, respectively, before the granulocytopenia was noted (cases 1 and 32). The depression in the proportion of granulocytes therefore cannot be definitely attributed to the drug.

In none of the reported series has the blood been studied through the period of the rash. Only occasionally has there been mention of the fact that readministration of the drug at a later date produces a sharp febrile response with the development of a diffuse erythematous eruption. The fate of patients who have once had a sulfanilamide rash is not known. Studies made on such patients during the eruption and after varying intervals should be of practical interest in view of the widespread use of the drug. In addition, the theoretic importance of such studies in providing data on the mechanisms of reactions to drugs in general must not be overlooked. The details of 10 cases investigated are therefore presented.

REPORT OF CASES

CASE 1.—J. E., a 7 year old boy weighing 22 Kg., was admitted to the hospital because of the recurrence of otitis media and because of drainage from the site of a postauricular abscess which had followed a mastoidectomy on the right. After four days the patient became afebrile, but, because of the presence of Streptococcus haemolyticus in the discharge, sulfanilamide was administered in a daily dose of 3.6 Gm. Prior to this, the child's total leukocyte count was 9,300, with 75 per cent polymorphonuclears and 4 per cent eosinophils. On the eighth day of therapy his temperature rose to 100 F. On the following day there was a sharp rise in temperature to 103 F. with the appearance of a discrete maculopapular eruption, at which time the drug was discontinued. The rash lasted for forty-eight hours. The concentration of sulfanilamide in the blood was 5.5 mg. per hundred cubic centimeters.[12] At this time mild generalized lymphadenopathy was noted, with slight enlargement of the liver. A hard splenic edge could be felt 2 cm. below the costal margin in the midclavicular line. These findings persisted for about two weeks. Blood counts were not made during the height of the eruption, but as the eruption was subsiding a total leukocyte count of 4,800 with 35 per cent polymorphonuclears was recorded.

Eight days after the disappearance of the eruption, the patient was given a test dose of 0.6 Gm. of sulfanilamide by mouth. Within an hour and a half he complained of severe frontal headache, and his cheeks became flushed. Thirty minutes later he began to vomit, with coincidental relief of the headache. Three hours after administration of the drug a deep flush was present over the face, chest and upper extremities; six hours after administration it had become intense over the entire body. The next morning all of these manifestations had disappeared, and the patient was again his normal self. The systemic response was accompanied by fever and leukocytosis (chart 1).

In an effort to determine whether the mode of administration would influence the type of response, 0.06 Gm. of sulfanilamide was given subcutaneously in a 1 per cent solution. After this the patient was drowsy for about four hours. A

12. The determinations of the concentration of sulfanilamide in the blood were performed by H. E. Stokinger according to the method of A. T. Fuller (Is *p*-Aminobenzenesulphonamide the Active Agent in Prontosil Therapy? Lancet **1**:194, 1937).

slight facial flush appeared, but there was no generalized eruption or fever. The total white blood count rose to a maximum of 11,800 from 8,000, and the percentage of polymorphonuclears showed an increase to 82 from 46, with subsequent return of both to their previous levels within twenty-four hours. Three days later 0.6 Gm. was administered subcutaneously, producing a reaction similar to that following the oral dose but not quite as severe. The number of white blood cells rose to 15,600, with 96 per cent polymorphonuclear leukocytes. There was a sharp rise in temperature, and the fever was accompanied by a generalized scarlatiniform rash, headache, drowsiness and vomiting. Again all these manifestations disappeared within twenty-four hours.

In order to find the smallest dose capable of producing the observed response, the patient was given by mouth gradually increasing doses starting with 0.06 Gm. Following each dose there was a slight increase in the number of polymorphonuclear leukocytes with only a minimal rise in temperature, 100.4 F. being the

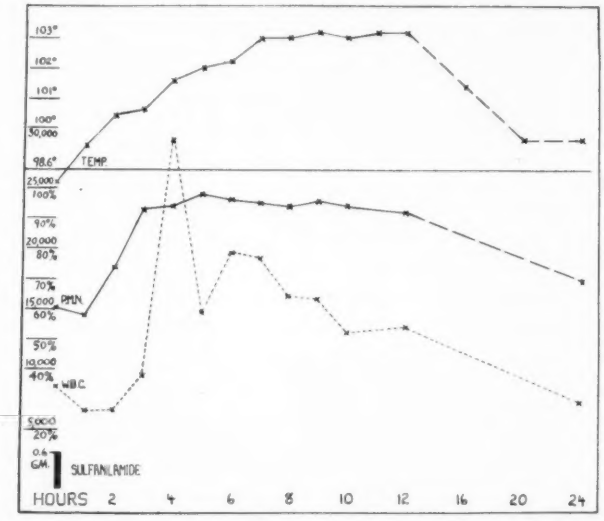

Chart 1 (case 1).—A typical reaction to a single dose of sulfanilamide eight days after disappearance of the original morbilliform eruption, illustrating the sharp febrile response with polymorphonuclear leukocytosis.

highest point reached. There were no cutaneous manifestations other than a malar flush. The patient was finally given the original dose of 0.6 Gm., again with only a slight response, i. e., a temperature of 100.2 F., a total white blood count of 11,300 with 81 per cent polymorphonuclears, a slight malar flush and no systemic complaints.

Having demonstrated a diminished response to sulfanilamide, the patient was immediately given 0.6 Gm. of the drug, and this dose was repeated every four hours. After two doses he became drowsy, and a temperature of 101 F. developed. The total leukocyte count rose to 13,000, with 77 per cent polymorphonuclears. An hour and a half after the third dose, although the temperature and the leukocytic picture had not changed, the patient complained of severe pains in both knees, the right wrist and the left elbow. No further sulfanilamide was administered; eight hours after the last dose there was still definite pain on motion of the knees and of the right wrist. At this time a crop of about twenty petechiae

was noted on the dorsum of each wrist. The arthritic phenomena subsided within twelve hours, after which the patient was discharged. During this time only slight polymorphonuclear leukocytosis was noted, and the liver and spleen were not palpable.

This patient, the first one studied in detail, demonstrated many important points: The eruption appeared after eight days of sulfanilamide therapy and was preceded by a prodromal elevation of temperature. Leukopenia was noted after the disappearance of the rash, even though the drug was discontinued as soon as the eruption was discovered. A marked difference in character was observed between the primary and the secondary eruption, in their morphology, in the size of dose necessary to produce them and in the length of time between administration and response. It was seen that the response could be elicited by parenteral as well as by oral administration. Giving small doses tended to ameliorate the effect, and gradually increasing the dose produced a relative diminution in response. Finally, resumption of the full dose brought about both arthritic and purpuric phenomena.

Case 2.—M. T., a 4 year old boy weighing 15.5 Kg., was admitted to the hospital because there had been a discharge from the right ear and a spiking temperature for ten days. The day after the child's admission a bilateral myringotomy was performed. The total leukocyte count was 13,500, with 74 per cent polymorphonuclears. With the report of a pure culture of Str. haemolyticus in the aural discharge, sulfanilamide therapy was begun, the dose being 3.6 Gm. daily. The temperature fell by lysis over a period of three days and did not go above 100 F. for the following five days. On the eighth day of treatment the temperature rose to 100.4 F., but no other abnormality was noted. The next day a morbilliform eruption appeared over the face; it spread successively over the chest, upper extremities, abdomen and lower extremities and disappeared in the same order, lasting in all seventy-two hours. During this time the temperature never rose above 101 F., and there were no constitutional symptoms despite continuation of the drug. The sulfanilamide concentration in the blood at the height of the eruption was 5 mg. per hundred cubic centimeters. After the rash subsided the temperature suddenly rose to 103 F., and an irregular fever persisted even though the dose was steadily decreased for fourteen days after its initiation (chart 2). At that time there was polymorphonuclear leukocytosis. Thereafter there was a steady fall in the total white blood count, with a corresponding decrease in the percentage of polymorphonuclear leukocytes; a final precipitous drop occurred when the sulfanilamide was discontinued. The leukocytes rose within the next forty-eight hours. The patient, clinically improved, was shortly afterward discharged.

Six days later the boy was readmitted to the hospital because of the recurrence of otorrhea and fever. Since conservative methods had not availed, a simple mastoidectomy was performed, from which the patient made an uneventful convalescence. In the latter part of this stay further studies were made on his reactions to sulfanilamide. Six weeks after the original appearance of the rash a test dose of 0.6 Gm. of the drug was administered. Three hours afterward the patient became nauseated and vomited, and an hour later a scarlatiniform eruption appeared over the face; it spread over the rest of the body in the next

four hours. The temperature rose to the high level of 103 F. during this period. Studies of the white blood count showed sharp polymorphonuclear leukocytosis, with a return to the previous level within twenty-four hours, as in the reaction illustrated in chart 1.

With the demonstration that the patient was still capable of reacting to the drug, sulfanilamide was given, the dose being 5 mg. at first and the amount increased over a period of twelve days to the original dose of 3.6 Gm. During this time the temperature never rose above 100.2 F.; the white blood count ranged between 9,000 and 12,000 and the percentage of polymorphonuclears between 50 and 69. At the conclusion of this period the sulfanilamide level in the blood was 9 mg. per hundred cubic centimeters.

On the child's subsequent admission, eight weeks later, sulfanilamide was readministered in the original daily dose of 3.6 Gm. The blood, studied over a period of three days, showed no significant alteration. There were no systemic or cutaneous manifestations, and the tourniquet test gave negative results. In the

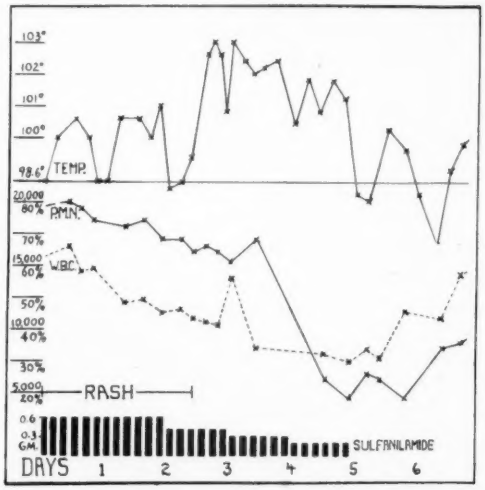

Chart 2 (case 2).—Course of reactions with continued administration of sulfanilamide after subsidence of the morbilliform eruption, showing the precipitate fall in the number of polymorphonuclear leukocytes. The graph starts on the ninth day of sulfanilamide therapy.

entire study, during three periods of residence, no clinical enlargement of the liver, spleen or lymph nodes was found; there were no purpuric phenomena, and no significant eosinophilia was discovered.

The data in this case emphasize primarily the discrepancy between the mildness of the symptoms during the initial eruption and the later marked granulocytopenia with continued administration of sulfanilamide. In addition there is to be noted the subsidence of the rash despite continuation of the drug, in contrast to the sharp febrile response with prostration following readministration after a free interval. It is of interest also that we were able later to give the full therapeutic dose

without untoward reactions by means of gradually increasing the dose and also to administer the drug subsequently without demonstrable effect.

CASE 3.—J. M., a 6 year old boy weighing 22 Kg., had been admitted to the hospital, three months before the present studies were contemplated, because of mastoiditis due to Str. haemolyticus. After he had been given 2.4 Gm. of sulfanilamide per day for nine days, a generalized morbilliform eruption developed. The concentration of sulfanilamide in the blood was 4.5 mg. per hundred cubic centimeters. Administration of the drug was stopped as soon as the eruption was noted, the rash disappearing thirty-six hours later. No studies of the leukocyte count were made at this time.

After an asymptomatic interval of three months the child was readmitted to the hospital for further investigation. Preliminary studies showed a total white blood cell count of 11,500 with 60 per cent polymorphonuclears. A tourniquet test (performed with the cuff maintained at a level 10 mm. of mercury lower than the level of the systolic blood pressure for four minutes) gave negative results.

The following morning administration of 0.45 Gm. of sulfanilamide every four hours was started. There was little change in the total white blood cell count, but the relative percentage of polymorphonuclears reached 86 in seven hours, falling slowly thereafter nearly to its previous level in forty-eight hours. The temperature rose to 101.6 F. seven hours after administration of the drug, and a generalized flush developed; this increased in depth and twenty-four hours later had become characteristically scarlatiniform. At this time a few petechiae were found scattered over the external surface of the body and over the mucous membranes. These increased in number during the next forty-eight hours. A tourniquet test performed as before showed 12 to 25 petechiae per square centimeter below the level of the cuff. The blood platelets numbered 224,000 per cubic millimeter. During the period of the eruption there were no systemic manifestations other than slight anorexia. The next morning, twenty-four hours after administration of the drug had been stopped, the rash had disappeared completely, the temperature was normal and the petechiae were fading. The patient was discharged. Two weeks later the tourniquet test gave negative results.

Three months later, during an admission to the hospital because of recurrent otitis media, full therapeutic doses of sulfanilamide were again given, and the white blood cell count was followed over a period of five days. Although there was a decrease in the number of polymorphonuclear leukocytes, the effect was not greater than that attributable to the subsidence of the infection. At this time there were no systemic or cutaneous manifestations. The results of the tourniquet test remained negative.

In this patient only the secondary manifestations were studied. The reaction produced three months after the original eruption was mild, but the rash was characteristically scarlatiniform and was accompanied by leukocytosis and fever. This was followed by evidence of capillary damage. Of especial importance is the fact that no untoward reaction was noted with full therapeutic dosage six months after the development of a typical morbilliform rash and three months after the production of scarlatiniform and purpuric eruptions.

CASE 4.—M. C., a 3 year old girl weighing 15.5 Kg., was admitted to the hospital with a history of difficulty in swallowing and swelling on the left side of the neck with a spiking temperature for three days. The liver and spleen could not be palpated on initial examination. The total leukocyte count was 27,900, with 80 per cent polymorphonuclear leukocytes. The next day two small vesicles were noted on the finger tips. On aspiration these yielded hemolytic streptococci. The blood culture, however, was negative. The patient was given 3 Gm. of sulfanilamide daily. The temperature fell gradually to normal during the next two days, and the swelling in the throat diminished.

On the sixth day of sulfanilamide therapy there was a transient rise in temperature to 101 F., and a diffuse but very faint generalized erythema without other systemic manifestations was noted. The sulfanilamide concentration in the blood was then 6 mg. per hundred cubic centimeters. The following day, when the

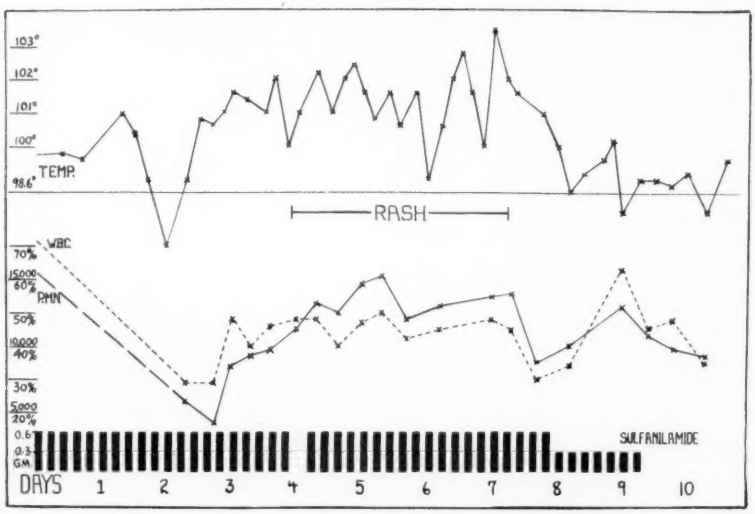

Chart 3 (case 4).—Course of reactions, demonstrating the transient leukopenia which preceded the rash, with slight granulocytopenia after the disappearance of the eruption. The graph starts on the fifth day of sulfanilamide therapy.

temperature had dropped sharply, the total leukocyte count was within normal limits, but the percentage of polymorphonuclears was only 16 (chart 3). The temperature again rose, and late that evening a prominent maculopapular eruption appeared over the cheeks, neck and upper extremities; this spread over the entire body in the next twenty-four hours. Fever persisted for five days longer. Despite the continued administration of sulfanilamide, the percentage of polymorphonuclears had been rising gradually, reaching 61 at the height of the eruption. The eosinophils numbered 6 per cent at the same time. The splenic edge was now easily palpable 3 cm. below the costal margin. There was no demonstrable enlargement of the liver. The cutaneous eruption faded in about seventy-two hours. With the disappearance of the rash secondary leukopenia was noted. At this time the patient started to vomit, and the daily dose of sulfanilamide was cut in half, i. e., to 1.5 Gm. The sulfanilamide concentration in the blood was 5.5 mg. per hundred cubic centimeters. Since the vomiting continued in the face of diminished

intake of the drug, sodium bicarbonate was given with sulfanilamide in equal amounts, with no relief; all medication was therefore canceled. The carbon dixoide-combining power of the plasma was 55 volumes per cent. Within twenty-four hours the vomiting had ceased, and the patient was discharged.

The following points in this case were significant: the preliminary depression in the number of granulocytes, with "escape" despite continued administration of the sulfanilamide; the prodromal elevation of temperature followed by the rash, with subsequent reappearance of leukopenia after the rash had faded, and the late intractable vomiting, which persisted as long as administration of the drug was continued.

Case 5.—A. R., a 10 year old boy weighing 35 Kg., who had had several admissions to the hospital because of infections of the upper respiratory tract with aural complications, was readmitted because of chronic otitis media and a discharging mastoid wound. In view of the presence of Str. haemolyticus in the cultures of material from the mastoid and the throat, the patient was given 3.6 Gm. of sulfanilamide per day. On the seventh day of therapy the temperature rose to 102.6 F.; it increased to 104 F. on the following day, a few hours before the appearance of a morbilliform eruption. Administration of the drug was stopped immediately when the rash was noted. Forty-eight hours later the patient was afebrile, and the rash had disappeared. Two days after this a test dose of 0.6 Gm. of sulfanilamide was given. Within four hours the temperature reached 103.4 F., and a diffuse itching scarlatiniform eruption appeared. The fever and eruption disappeared within twenty-four hours. No studies of the blood were made during this period.

Six months later the patient was readmitted to the hospital for further investigation. On admission the total leukocyte count was 9,800, with 54 per cent polymorphonuclears. The boy was given 0.6 Gm. of sulfanilamide. This was followed in four hours by a rise in temperature to 101 F., and a slight flush appeared over the malar eminences. The total leukocyte count reached the high level of 17,200, with 78 per cent polymorphonuclears. Since the initial response was slight, the patient was given the same dose every four hours on the following day. When the dose had totaled 2.4 Gm., the temperature rose to 101 F., and a slight generalized flush appeared. At this time, however, there was a prominent petechial eruption on the legs and on the dorsa of the feet, with a few similar lesions on the wrists. A tourniquet test with the sphygmomanometer cuff maintained at a level of 10 mm. below that of the systolic blood pressure for four minutes was productive of about three petechiae per square centimeter below the level of the cuff. This was considered evidence of decreased capillary resistance. The blood platelets at this time numbered 364,000 per cubic millimeter. The total white blood count was 9,600, with 78 per cent polymorphonuclears. Administration of the drug was stopped, and the patient was discharged. Two days after his discharge the tourniquet test was equivocal, the petechial eruption had almost faded, and the white blood count was 6,900, with 43 per cent polymorphonuclears. Three weeks later, when the patient reappeared in the outpatient department, the tourniquet test gave negative results.

In the study just described, the following points are to be emphasized: the prodromal fever, followed by a characteristic morbilliform eruption which occurred after eight days of sulfanilamide therapy; the

scarlatiniform eruption resulting from a single dose after a few days, and the mild febrile reaction with polymorphonuclear leukocytosis six months later, followed by purpuric phenomena with evidence of decreased capillary resistance.

CASE 6.—A. M., an 11 year old girl weighing 45 Kg., was admitted to the hospital because of a discharging and painful left ear. Culture of the discharge showed Str. haemolyticus. The total leukocyte count on the patient's admission was 10,000, with 74 per cent polymorphonuclears. Sulfanilamide was administered in a daily dose of 3.6 Gm. This medication was accompanied by alleviation of symptoms. On the seventh day of treatment a low grade fever was discovered; it was followed thirty-six hours later by the appearance of a maculopapular eruption over the face and the upper extremities. The total white blood cell count at the onset of the eruption was 9,000, with 77 per cent polymorphonuclears. The rash spread over the remainder of the body, lasting ninety-six hours in all. Because of uncertainty as to whether the febrile reaction was due to the drug or to an aural complication, the sulfanilamide was discontinued forty-eight hours after the rash was noted. The percentage of polymorphonuclear leukocytes gradually fell, being 40 at the time the rash had completely faded and reaching the low level of 35 two days later. The proportion of polymorphonuclears gradually returned to 54 per cent after five days. The total count during this period varied between 6,400 and 9,000, roughly paralleling the proportion of granulocytes. The highest eosinophil count during the time of observation was 4 per cent. No lymphadenopathy or enlargement of the liver or spleen was noted.

In this patient we noticed the appearance of the characteristic eruption following eight days of therapy, preceded by a prodromal period of fever. The depression in the number of polymorphonuclear leukocytes, which was first noticed as the rash faded, persisted for forty-eight hours even though the drug had been discontinued.

CASE 7.—M. O'B., a 2½ year old boy weighing 15 Kg., was admitted to the hospital because of a history of discharge from the ears for two days after myringotomy. The total white blood cell count was 7,900, with 73 per cent polymorphonuclear leukocytes. In view of the presence of hemolytic streptococci in the aural discharge, administration of sulfanilamide was started with a daily maintenance dose of 1.5 Gm. The patient ran a spiking temperature, which rose to 104 F., for the first forty-eight hours; it then fell by lysis, and the otorrhea diminished. A single blood count taken on the eighth day of therapy showed a total of 10,500 leukocytes, of which 38 per cent were polymorphonuclears. There were no cutaneous manifestations, and since the patient appeared to be fairly well the sulfanilamide was continued as before.

Five days later there was a sudden sharp rise in temperature, and a diffuse blush with erythematous macules appeared. The white blood cell count at that time was 12,900 with 69 per cent polymorphonuclear leukocytes. The rash faded within the next forty-eight hours, and the total leukocyte count fell to the low level of 7,200, with 31 per cent polymorphonuclears, two days after the rash had faded. Thereafter the relative percentage of granulocytes rose gradually, the total count remaining about the same, and therapy was stopped. After this the leukocyte count continued to rise.

Ten days later, after the percentage of polymorphonuclear leukocytes had remained between 55 and 60 over a four day period, 0.3 Gm. of sulfanilamide was administered in a single dose. This was followed by a rise in the total white count from 7,600 to 11,600, and in the polymorphonuclear leukocytes from 59 to 85 per cent, with a subsequent decrease to levels within the patient's usual range. Although further studies were made, we felt that the occurrence of a complicating infection invalidated later results.

This case is interesting in that a decrease in the number of granulocytes was noted three days before the appearance of an eruption and was followed by an escape during the febrile period, when the rash was manifest. After the subsidence of the eruption secondary granulocytopenia was noted, followed again by a rise. The reaction to later administration of a single dose of sulfanilamide was slight. Only moderate polymorphonuclear leukocytosis without any systemic phenomena was found.

CASE 8.—N. B., a 6 year old Puerto Rican girl weighing 28 Kg., was admitted to the hospital because of discharge from the left ear and fever. Cultures of the aural discharge showed Str. haemolyticus, and administration of sulfanilamide was started in a daily dose of 3 Gm. Despite sulfanilamide therapy the discharge persisted, although the temperature returned to normal, and simple mastoidectomy was performed on the seventh day of administration of the drug. The sulfanilamide therapy was stopped for twenty-four hours postoperatively and was then resumed in the previous dose. On the day following operation the patient's temperature rose to 101 F. and twenty-four hours after that to 102 F. The next morning the drug was discontinued because of uncertainty as to the cause of the fever. On the day after medication was stopped the temperature fell to 100 F., but a blotchy erythematous eruption appeared over the face and, in scattered small papules, over the body; this rash was unlike that seen in other cases. The eruption faded completely in seventy-two hours, the patient being afebrile during this time.

The total leukocyte count, which had been 7,300 with 68 per cent polymorphonuclear leukocytes on the girl's admission, reached a level of 5,000 with 78 per cent polymorphonuclears on the day prior to the eruption and fell gradually thereafter, reaching a level of 4,200 with 50 per cent polymorphonuclears forty-eight hours after the disappearance of the rash. At this time the eosinophils had increased to 3 per cent, the highest level reached, and the liver and spleen were not palpable. The tourniquet test, with the pressure of the cuff maintained for four minutes at a level of 10 mm. of mercury below that of the systolic blood pressure, gave negative results.

Eight days later, when the total white blood cell count had become stabilized between 5,000 and 8,000 and the relative percentage of polymorphonuclears between 65 and 72, the patient was again given 3 Gm. of sulfanilamide in divided doses. Eight hours after the first dose was given, a blotchy erythematous eruption was again noted, and the temperature rose to 102 F. The fever and eruption disappeared the following morning, despite continued administration of the drug. A few scattered petechiae were noted on the skin and on the buccal mucosae. The platelet count at this time was 284,000 per cubic millimeter. The drug therapy was stopped on the third day, and twenty-four hours later a markedly positive reaction to the tourniquet test was obtained. The leukocyte count reached the high level of 16,600, with 84 per cent polymorphonuclears, at the height of the eruption and fever, returning to its previous level within twenty-four hours and not changing significantly thereafter.

Of interest in this case are these points: the appearance of an unusually discrete papular eruption preceded by a possibly prodromal rise in temperature; the development of the rash when the sulfanilamide had been discontinued and the temperature was falling, and questionable granulocytopenia manifesting itself after the subsidence of the eruption. Although the second, experimentally invoked, eruption was similar in form to the first, there was leukocytosis with the second rash, and no subsequent leukopenia was observed. The evidence of increased capillary fragility was definite, although there were only a few spontaneous petechiae. This patient is not thought to have had significant granulocytopenia.

Case 9.—A. W., a 5 year old girl weighing 16.5 Kg., was admitted to the hospital because of purulent otitis media due to Str. haemolyticus. The liver and spleen were not palpated on her admission. She was given 3.6 Gm. of sulfanilamide daily. On the eighth day of therapy the temperature rose to 104 F., and she was lethargic and irritable. The following day a morbilliform eruption appeared, and administration of the drug was stopped. The concentration of sulfanilamide in the blood was 2.3 mg. per hundred cubic centimeters. The edge of the liver, which was soft, was felt 1.5 cm. below the costal margin. The splenic edge was hard and sharp and extended 3 cm. below the costal margin on deep inspiration. The rash lasted for thirty-six hours, during which time the patient became afebrile. The total white blood count, which had been 50,000 with 81 per cent polymorphonuclear leukocytes on the child's admission, was 9,000 with 75 per cent polymorphonuclears on the day prior to the outbreak of the eruption. On the day after the disappearance of the rash the leukocyte count was 8,900, with 47 per cent polymorphonuclears. The girl was seen subsequently in the outpatient department. Ten days after they were originally felt, the liver and spleen were no longer palpable, and the number of white blood cells had become stabilized between 9,000 and 11,000, with 50 to 65 per cent polymorphonuclears.

This case is included because of the striking splenomegaly and the slight enlargement of the liver which occurred during the period of the eruption, even though the leukocytes were not specially studied and the routine counts recorded are inconclusive.

Case 10.—E. S., a 9 year old girl weighing 39 Kg., was admitted to the hospital because of a postauricular abscess at the site of an old mastoidectomy scar. The total white count was 9,400, with 66 per cent polymorphonuclears. On the day following the patient's admission incision of the abscess yielded pus, from which a pure culture of Pneumococcus type III was grown. Administration of sulfanilamide was started, the maintenance dose being 3.6 Gm. per day. Beginning four days later, a daily rise in temperature was noted, the reading being 101 F. on the seventh day. On the ninth day the temperature rose to 102.4 F., and a morbilliform eruption appeared. The patient complained of a slight headache. With the appearance of the rash the drug therapy was stopped, and the rash faded in forty-eight hours, with gradual defervescence to normal by the end of that time.

The leukocytic picture was studied for six days, starting forty-eight hours before the onset of the morbilliform eruption. At the beginning of this period

the total white blood count was 8,200, with 75 per cent polymorphonuclears; the latter reached a maximum of 80 per cent when the rash appeared, gradually fell, being 43 per cent by the time the rash had faded (i. e., forty-eight hours after the sulfanilamide therapy had been stopped), and rose again to 54 per cent a day later. The white blood cell count closely paralleled the percentage of polymorphonuclears, ranging between 4,100 and 11,700. The eosinophils never comprised more than 1 per cent of the total. No enlargement of the liver or spleen was observed.

In this patient there was again noted the prodromal febrile period. The cutaneous manifestations appeared nine days after the commencement of sulfanilamide therapy. There was subsequently transient leukopenia, even though the drug had been discontinued.

COMMENT

I. *"Natural History" of the Reactions.*—From the cases investigated and from a review of the literature we have attempted to form a composite picture, grouping together the sequence of events to build a "natural history" of the abnormal reactions in the patients under consideration. Such a schema must be accepted only in the broadest sense, the individual variations being wide.

The eruption itself, appearing within five to seventeen days, has been noted occasionally to be preceded by transient leukopenia (cases 4 and 7 and chart 3), accompanied by slight but definite erythema. In all of our cases there was a prodromal period of fever, ranging from three to seventy-two hours, which continued until the appearance of the eruption. The morbilliform eruption was consistently accompanied by some degree of fever, with the white blood counts within or above normal limits. Three of 8 patients (cases 1, 4, and 9) examined during the initial eruption showed palpable enlargement of the spleen, the splenomegaly being no longer demonstrable after two weeks. In previously reported cases there has been an occasional hemorrhagic element in the eruption.

The rash lasted from thirty-six to ninety-six hours, tending to persist for the longer period in those cases in which the drug was continued. In 4 cases (cases 4, 6, 7 and 9) leukopenia developed as the rash was fading or shortly afterward, irrespective of continuation of sulfanilamide. In 2 others (cases 1 and 10) a single count made shortly after the disappearance of the rash showed granulocytopenia. In only 1 instance (case 8) was there no significant depression of the granulocytes. One patient (case 4) had persistent vomiting which began on the fourteenth day of therapy, twenty-four hours after the rash had faded. In 1 further case (case 2, chart 2), in which the drug was continued without causing vomiting, the patient showed persistent fever and leukopenia. No significant eosinophilia occurred in any case.

After varying intervals, readministration of the drug caused a totally different reaction. A single large dose resulted in a sharp febrile response within a few hours and in polymorphonuclear leukocytosis, often associated with malaise, nausea, vomiting, headache and drowsiness and nearly always accompanied by a brilliant scarlatiniform eruption which faded within twenty-four hours (chart 1). On the other hand, the effect of small doses (cases 1 and 2) was to produce slight polymorphonuclear leukocytosis and a mild elevation of temperature, but no systemic complaints or cutaneous manifestations other than some flushing of the cheeks. The type of reaction was found to be independent of the mode of administration of the drug (case 1).

Continued administration after an interval following the original morbilliform eruption produced purpuric manifestations with evidences of increased capillary fragility without thrombocytopenia (cases 3, 5 and 8). In 1 case petechiae and arthritic phenomena were observed simultaneously, but no studies were made of the blood platelets or of the capillary fragility (case 1).

The diminution or loss of the abnormal reactivity seemed to be influenced by several factors. In general, the passage of time tended to ameliorate the response. Administraion of several large doses of the drug resulted in abolition of the untoward reactions. Gradually increasing the doses during a comparatively short period likewise produced failure to respond. Finally, in 2 patients (cases 2 and 3) in whom a decrease in or absence of response had been obtained by gradually increasing doses or by repeated large doses, readministration in full therapeutic quantities after a longer interval caused no demonstrable change in the temperature or in the leukocyte picture, nor were there any systemic manifestations.

II. *Analogies with Reactions to Other Drugs.*—In a brief review of the literature on reactions to drugs we have noted several points of similarity between the sulfanilamide group of drugs and other compounds. A morbilliform eruption has often been described as following the administration of barbituric acid and its derivatives. Such reactions occur, but less frequently, with the arsenicals. In rare instances the use of antipyrine gives rise to a morbilliform eruption with concomitant purpuric manifestations. Purpura resulting from administration of drugs has been found due in some instances to thrombocytopenia and in others to direct damage to the capillary endothelium. With the arsenicals and gold compounds, both of these factors appear to be involved. Iodine apparently acts directly by increasing capillary fragility.

It has been commonly accepted that compounds containing the benzene ring exhibit a depressant action on the leukocyte count. Sulfanilamide, containing as it does this radical, might produce this reaction and

has done so. However, the transient leukopenia following the morbilliform eruption probably has no relation to the presence of the benzene ring.

Leichtentritt and others [13] have described a sequence of events following the administration of nirvanol (the sodium salt of phenylethylhydantoin) which resembles that found in our study of sulfanilamide. They pointed out the slight leukopenia preceding the outbreak of the eruption, the latter appearing after a fairly constant interval. With the development of the rash, the white blood cell count returned to normal levels or there was polymorphonuclear leukocytosis with eosinophilia. With the disappearance of the rash transient leukopenia supervened. Schwarz [14] described altered reactions to readministration of the drug.

III. *Mechanism of the Abnormal Reaction.*—Although the initial eruption due to sulfanilamide resembles that produced by other drugs, the mechanism of the abnormal reaction remains equally obscure with all. Attempts to demonstrate antibodies to sulfanilamide by cutaneous tests, precipitin reactions and passive transfer in human beings and in guinea pigs have been unsuccessful [8] during and after the usual morbilliform eruption. Two reports, one of exfoliative dermatitis [15] and the other [16] of a peculiar reaction ascribed to sulfanilamide and characterized by pruritus, lacrimation, sneezing and shortness of breath, make mention of positive reactions to the drug in patch tests but do not describe them in detail.

In an attempt to find a material for testing during the early part of our studies, human serum protein was coupled to diazotized sulfanilamide in an alkaline medium. The conjugated protein should theoretically have possessed the specificity of sulfanilamide alone when used as a test material in human beings. Intradermal tests with this new protein compound in patients during the initial eruption and for two weeks afterward gave uniformly negative results. Precipitin tests with the same protein against the serum of these patients also gave negative reactions. Likewise passive transfer experiments, utilizing the guinea pig uterus according to Dale's technic as previously employed with proteins coupled to diazotized antipyrine,[17] gave negative results.

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13. Leichtentritt, B.; Lengsfeld, W., and Silberberg, O.: Klinisches und Experimentelles zur Nirvanoltherapie bei der Chorea minor im Kindesalter, Jahrb. f. Kinderh. **122**:12, 1928.

14. Schwarz, E.: Veränderungen des leukozytären Blutbildes durch Nirvanolbehandlung bei choreatischen Kindern, Arch. f. Kinderh. **94**:1, 1931.

15. Myers, G. B.; Vonder Heide, E. C., and Balcerski, M.: Exfoliative Dermatitis Following Sulfanilamide, J. A. M. A. **109**:1983 (Dec. 11) 1937.

16. Salvin, M.: Hypersensitivity to Sulfanilamide, J. A. M. A. **109**:1038 (Sept. 25) 1937.

17. Mulinos, M. G., and Schlesinger, E. R.: A Contribution to Drug Allergy: Antipyrine, Proc. Soc. Exper. Biol. & Med. **35**:305, 1936.

That such results should not have been unexpected is suggested by sensitization experiments in guinea pigs as performed by Nitti and Bovet.[18] These investigators, following Landsteiner's method, gave repeated small intradermal injections of prontosil to a batch of normal guinea pigs. When a dilute solution of prontosil was later placed on the skin of these animals, they showed a marked reaction. A group of animals treated similarly with sulfanilamide did not have a heightened reaction to the drug later. Sulfanilamide furthermore caused no reaction in the skin of animals made hypersensitive to prontosil, and, conversely, prontosil in solution had no effect on the animals treated with sulfanilamide, which showed that sulfanilamide itself could neither sensitize a guinea pig nor produce a cutaneous reaction in an animal sensitized to prontosil. Bovet [19] later used this reaction as an argument in favor of the decomposition of prontosil into sulfanilamide and 1,2,4-triaminobenzene, by demonstrating that guinea pigs sensitized to prontosil gave a heightened cutaneous reaction to the latter breakdown product. A clinical illustration of these reactions is the occurrence of occupational dermatitis among workers in a plant which produces prontosil.[20]

Although the reactions in these experiments throw light on eczematoid reactions with prontosil, they do not appear to be closely related to the transient morbilliform eruption and the later purpuric and other phenomena which accompany prolonged sulfanilamide therapy. The dose of the drug apparently plays a significant role in the production of the morbilliform eruptions. Analysis of the data presented by Gallagher [21] shows that eruptions developed in 5 of 14 boys who received 5.4 Gm. or more of sulfanilamide for a minimum of five days, whereas no eruptions occurred among 11 boys who received 2.4 Gm. or less of the drug daily for the same period of time. The suggestion that the reaction resembles serum disease closely does not help much in explaining it.

SUMMARY

The literature regarding the morbilliform eruption due to sulfanilamide has been reviewed with especial attention to the concomitant leukocytic response and to subsequent reactions.

18. Nitti, F., and Bovet, D.: Recherches expérimentales sur les phénomènes allergiques provoqués par la sulfamidochrysoïdine (prontosil), Rev. immunol. **2**:460, 1936.

19. Bovet, D.: Recherches expérimentales dans le domaine de la chimiothérapie des infections bactériennes, Schweiz. med. Wchnschr. **18**:288, 1937.

20. Sézary, A., and Horowitz, A.: Intolérance professionelle (eczéma) causée par la sulfamido-chrysoïdine (rubiazol), Bull. et mém. Soc. méd. d. hôp. de Paris **60**:767, 1936.

21. Gallagher, J. R.: Observations on the Therapeutic Value of Sulphanilamide in Beta Hemolytic Streptococcus Pharyngitis, Am. J. M. Sc. **194**:830, 1937.

Ten cases have been studied to determine the nature of the eruption, the course and the picture given by the white blood cells, together with later manifestations.

A "natural history" of the eruption has been proposed: This emphasizes prodromal fever, sometimes preceded by transient leukopenia and followed by a morbilliform rash, often with splenomegaly, the eruption developing within five to seventeen days after commencement of sulfanilamide therapy and lasting from thirty-six to ninety-six hours. Subsequent secondary leukopenia has been observed. Later administration of the drug has produced a characteristic scarlatiniform rash with fever and leukocytosis within a few hours; continued administration has been associated with evidence of increased capillary fragility and occasionally with arthritic phenomena. Passage of time, gradual increment of the dose over a short period, or repeated administration of large doses at intervals has decreased or abolished the reactivity.

Attempts to correlate these reactions with reactions to other drugs have been made. The closest parallel found is the clinical picture of "nirvanol (sodium phenylethylhydantoin) sickness."

Efforts to elucidate the mechanism of the reactions under consideration have been unsuccessful.

ACTION OF ERGOSTEROL AND OF PURIFIED VITAMIN D ON POLIOMYELITIS VIRUS

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It has been shown that cholesterol inactivates the virus of poliomyelitis either by adsorption or by destruction.[1] Cholesterol is derived from animal sources. Perhaps ergosterol would act likewise. The latter is obtained from ergot or yeast and has the same hydrocarbon filament as cholesterol, but with an additional methyl group in the side chain and with two additional double bonds, one in the side chain and the other in the nucleus.

METHODS AND MATERIALS

In the following experiments, the same technic was employed as in previous experiments with cholesterol.[1]

A quantity of a 1 per cent suspension of Flexner's eluted mixed virus[2] together with a quantity of ergosterol[3] equal in weight to 10 per cent of the total volume used was ground for twelve hours in a ball mill that had been placed in the refrigerator. The test dose was 0.15 cc. of the supernatant fluid which remained after centrifugation at high speed for thirty minutes. This dose represented a 50 per cent increase over that of 0.1 cc., the dose that in 1936 regularly produced quadriplegia in the susceptible monkey. The virus used for control animals was always from the same lot, ground at the same time, at the same speed, and attached to the same ball mill.

In all the experiments described, the virus used was Flexner's mixed virus strain. All injections were made intracerebrally under general anesthesia. The animals used were Macacus rhesus monkeys.

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From the Department of Pediatrics of Western Reserve University and the Division of Contagious Diseases of City Hospital.

1. Toomey, J. A.: Adsorption of the Poliomyelitis Virus by Cholesterol, Am. J. Dis. Child. **54**:1272 (Dec.) 1937.

2. Schaeffer, M., and Brebner, W. B.: Purification of the Poliomyelitis Virus, Arch. Path. **15**:221 (Feb.) 1933. Sabin, A. B.: Experiments on the Purification and Concentration of the Virus of Poliomyelitis, J. Exper. Med. **56**:307 (Sept.) 1932.

3. The ergosterol was furnished by Parke, Davis & Co. of Detroit.

EXPERIMENTS

Part 1.—Three monkeys were given injections of the ergosterol-treated virus, and 3 controls of the plain virus. Two animals of the first group had only weakness of the leg muscles; the third animal had paralysis of the muscles of both legs and weakness of the arm muscles. In the 3 controls, quadriplegia developed.

Fully a year later, two other sets of animals were tested. The preparation of the virus was the same, but its virulence had decreased, so that the dose injected had to be larger in order to produce quadriplegia in the control monkeys. Care was taken to avoid the layer which had collected at the top after centrifuging. The center fluid was withdrawn and further centrifuged until clear. Three monkeys were given an injection of 0.4 cc. of the ergosterol-treated virus, while 3 controls received 0.4 cc. each of the untreated virus. Except for an almost imperceptible weakness in 1 of the animals which had received the ergosterol-treated virus, all 3 escaped the disease, while in the 3 controls quadriplegia developed.

Thus it is seen that ergosterol, like cholesterol, inactivates the virus of poliomyelitis.

Part 2.—The foregoing experiments were performed using purified and eluted virus. Coincident with other experiments in 1936, another lot of the same virus, but unpurified, was treated as the purified virus had been, one part of the lot being treated with irradiated and two parts with nonirradiated ergosterol. Three monkeys were inoculated, 1 with each part of the lot; in all quadriplegia promptly developed.

This suggests that when the virus is left in combination with nervous tissue, it is neither adsorbed nor destroyed by ergosterol.

A year later, this experiment was repeated with some modification of the procedure. The virus suspension was made up as usual, but the suspension was centrifuged to get rid of the larger particles of cord tissue and to secure a more homogeneous suspension of virus. The procedure was the same except that ergosterol was added to one lot of unpurified virus and cholesterol to another. A dose of 0.4 cc. of ergosterol-treated, unpurified virus was injected into each of 2 animals. A dose of 0.4 cc. of cholesterol-treated, unpurified virus was injected into each of 2 animals. A dose of 0.4 cc. of unpurified virus was injected into each of 2 animals. In all the monkeys complete quadriplegia developed.

This experiment confirms again that neither cholesterol nor ergosterol adsorbs or destroys virus held in combination with cord tissue.

Part 3.—Perhaps a more purified vitamin D product could inactivate, kill or adsorb the virus more efficiently. Drisdol [4] (crystalline

4. The drisdol was obtained from the Winthrop Chemical Co. of Rensselaer, N. Y.

vitamin D in propylene glycol) was used as the source of purified vitamin D. This crystalline vitamin D differs from ergosterol and cholesterol in that the phenanthrene ring system of the sterols has been opened and a more saturated compound formed which has three conjugated double bonds and one double bond in the side chain.

Late in 1936, equal quantities of drisdol and a 2 per cent suspension of virus were combined and shaken for a few minutes; 0.1 cc. was injected into a monkey. A control animal was given 0.1 cc. of a 1 per cent suspension of plain virus. Quadriplegia developed in both animals.

Perhaps more contact between virus and drisdol was needed. Equal quantities of 2 per cent virus and drisdol were mixed and ground for five hours, and 0.1 cc. was injected into a monkey. A control animal received 0.1 cc. of a 1 per cent suspension of plain virus. The former animal showed "furring," while in the control poliomyelitis developed. This experiment was repeated. One animal received the suspension of prepared virus and another that of the plain virus. The former escaped the disease, and the latter showed pareses of both legs. The results of the last experiment were inconclusive. The experiment was repeated in 4 more monkeys, 2 of which were controls. In all 4 animals poliomyelitis developed.

It was not too definite whether activated material could inactivate virus, although the results obtained from the experiments suggested that it could. It was certain, however, that drisdol was no more virucidal than plain ergosterol or cholesterol. Perhaps its menstruum, propylene glycol, prevented exposure of the rays to the virus; perhaps enough of the colloid had not come in contact with the virus, or the added amount of material was insufficient to affect the virus completely.

Because of possible objections to the use of crystalline vitamin D in propylene glycol, it was decided to work with crystalline vitamin D itself. In the manufacture of the latter,[5] nothing is removed from the ergosterol.[6] Its activity is the result of an intramolecular rearrangement of the molecule.

Ten cubic centimeters of eluted virus was combined with 100 mg. of crystalline vitamin D. Ten cubic centimeters of eluted virus was also centrifuged. The upper portion of the vitamin D prepartion was discarded, and 4 animals were each given an injection of 0.2 cc. of a 1 per cent suspension of prepared virus. Of these, 1 animal escaped the disease; 1 had a mild attack of it and 2 had quadriplegia. Four control animals were inoculated with 0.2 cc. of a 1 per cent suspension of purified virus. All had quadriplegia.

Again, the results were only suggestive, though apparently in the right direction. It might have been that the quantity of activated colloid

5. Barlow, O. W.: Personal communication to the authors, July 24, 1937.

6. Puetzer, B.: Personal communication to the authors, July 24, 1937.

used was not enough. When virus was prepared for the next experiment, it was ground with increased quantities of crystalline vitamin D.

Three lots of 10 cc. of 1 per cent virus were taken; one lot was purified and ground with 1 Gm. of crystalline vitamin D for twelve hours, one lot was purified and ground, and one lot was ground unpurified, as it was. A dose of 0.1 cc. of each virus suspension was injected into separate monkeys. The animal which received the crystalline vitamin D virus suspension had transient weakness. The one which received the purified virus alone had paraplegia, and the animal which received the unpurified virus had quadriplegia.

The results were inconclusive. At this point, our stock virus began to be less potent, so that a new minimal paralyzing dose had to be established. This was found to be from 0.4 cc. to 0.5 cc. of a 1 per cent suspension of virus. A quantity of virus was prepared and divided into two lots, one lot being treated with crystalline vitamin D, as described under "Methods and Materials," and one untreated. Three animals were each given an injection of 0.4 cc. of the treated suspension, and 3 controls, of 0.4 cc. of the suspension of plain virus. Save for slight weaknesses, all the animals in the former group escaped, while all the controls had quadriplegia.

It is seen that inactivation of the virus takes place when enough crystalline vitamin D is used.

Part 4.—Late in 1937, it was decided to determine the comparative effect of ergosterol and cholesterol on suspensions of purified virus. A quantity of virus was prepared and divided into three lots. One lot was treated with ergosterol and one with cholesterol, and one was not treated. Six animals were inoculated, 0.4 cc. of each lot being employed in each of 2 animals. The animals inoculated with the virus that had been treated with ergosterol or cholesterol escaped the disease, while the 2 controls had it.

Apparently, ergosterol as well as cholesterol can inactivate virus.

Part 5.—Poliomyelitis virus when purified is finally eluted in a fifteenth-molar solution of dibasic sodium phosphate. The addition of this base to sterol products could not release a free alcohol which in itself would destroy virus. Examination of the chemical qualities shows that all of these sterols are alcohols, as is purified crystalline vitamin D. If inactivation were due to a high alcoholic content, then drisdol carried in propylene glycol, a diol of the formula $CH_2CH_2OH.CH_2OH$ and hence containing more alcoholic groups,[6] should kill virus more easily. This is the reverse of our observation.

To make certain, however, and to determine the effect of a fifteenth-molar solution of dibasic sodium phosphate ground with cholesterol, the following experiments were performed.

A 2 per cent suspension of virus in saline solution was adsorbed to aluminum hydroxide in the presence of potassium acid phosphate and eluted out with cholesterolized dibasic sodium phosphate. Cholesterolized dibasic sodium phosphate was obtained as follows: Five grams of cholesterol was added to 50 cc. of a fifteenth-molar solution of dibasic sodium phosphate. This combination was ground in a ball mill for twelve hours, centrifuged, shaken vigorously with an equal quantity of 2 per cent purified virus, and allowed to stand for two hours. A dose of 0.4 cc. was then injected into a monkey, while a control animal received 0.4 cc. of purified virus. (Cholesterol instead of ergosterol was used in these experiments.) The animal inoculated with the treated virus had quadriplegia. Quadriplegia also developed in the control animal.

This experiment was repeated. Two animals were given the treated virus. The disease developed and they had quadriplegia, 1 on the seventh and the other on the ninth day. Of 2 controls, 1 showed quadriplegia on the eighth day and the other paraplegia on the tenth day.

Thus it is obvious that grinding cholesterol in a fifteenth-molar solution of dibasic sodium phosphate does not produce a substance which can destroy the virus when added to a virus suspension.

Part 6.—The material as prepared in part 5 should have been ground together with the suspension of purified virus for a period of twelve hours, as was done in the original experiments with cholesterol and ergosterol virus preparations. The next experiments were done with this objection in mind.

The virus was ground as previously; the aluminum gel was added in the presence of potassium acid phosphate (K_2HPO_4), and the combination was allowed to stand four hours and then centrifuged. The virus was left in the gel and the liquid decanted. The tube was carefully washed of sediment inside and on the top to get rid of any acid, and the gel combination was resuspended in dibasic sodium phosphate. This stood for twelve hours and then was shaken and centrifuged, yielding a 2 per cent purified virus in the eluate. Meanwhile, cholesterol had been ground in dibasic sodium phosphate. As in the first experiment of part 5, this mixture had been ground for twelve hours, after which it was centrifuged and the fluid decanted. Equal quantities of this fluid and the 2 per cent purified virus were mixed together and ground for twelve hours more.

The treated purified virus was injected into 2 animals and the purified virus into 2 controls. The dose was 0.4 cc. One animal inoculated with treated virus came down with the disease on the ninth day and had quadriplegia on the eleventh; the other came down with the disease on the ninth day and showed paraplegia of the lower extremities by the fourteenth day. One control animal began to have paresis on the eighth day and had paraplegia on the ninth day. The other control had weak-

ness on the ninth day, but nothing more than weaknesses of the muscles of both upper and lower extremities ever developed.

This experiment was repeated. Two animals were inoculated with treated purified virus and 2 controls with purified virus. In both the animals that received the treated virus the disease began to develop on the eighth day; 1 had quadriplegia on the ninth and the other on the tenth day. Both the 2 controls began to show symptoms of the disease on the eighth day; both had paraplegia on the ninth and quadriplegia on the tenth day.

CONCLUSION

Thus, the chemicals used in the preparation of eluted virus did not produce a material which in itself destroys virus. Since it has been previously shown that the mechanical act of grinding does not affect the virus,[1] one can conclude that the effect on the virus must be produced by these sterol products themselves.

It has been previously noted that cholesterol inactivates suspensions of purified poliomyelitis virus. It is now shown that ergosterol and crystalline vitamin D in certain amounts accomplish the same end. Ergosterol, like cholesterol, does not inactivate unpurified poliomyelitis virus.

HORMONAL REACTIONS OF PREGNANCY

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The name and definition of hormonal reactions of pregnancy originated with Halban.[1] His definition outlined the origin of two neonatal phenomena, namely, physiologic neonatal mastitis and physiologic neonatal vaginal bleeding.

The first phenomenon is well known: The mammae of the newborn child (each originally consists of ten to fifteen radially arranged mammae, the entire glandular mass being approximately 5 to 10 mm. in diameter) begin to grow on the third or fourth day after birth and on the fifth or sixth, more often on the eighth to the twelfth, surpass their original size many times; externally they appear swollen. A substance at first thin and watery, later yellowish and milky, like colostrum in composition (popularly called witches' milk), can be pressed from them. The swelling disappears within two to three weeks; it rarely lasts from one to two months. Vaginal bleeding of newborn infants is less frequent than the phenomenon just described. A bloody discharge mixed with pus begins to flow from the vagina. A more accurate examination reveals that the source of the blood is not the vagina but the uterus; "vaginal bleeding" is therefore a misnomer. The bleeding is similar to menstruation.

Halban explained the occurrence of the two phenomena as follows: Those hormones which govern the maternal development during pregnancy or secretion of the milk, on the one hand, and periodic bleeding, on the other, enter the fetal organism through the placenta, causing similar but of course less marked reactions in the newborn infant. Therefore, he named the two phenomena hormonal reactions of pregnancy. The name and the explanation found universal acceptance in the literature, although at the time there were no tangible proofs of diaplacental passage of hormones.

Since then the hormones in question have been isolated, and chemical and biologic tests have been developed to prove their presence. With these methods, some authors demonstrated that great quantities of gonadotropic and estrogenic hormones can be found in the blood

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Report of the Royal Hungarian State Orphans' Asylum; Director and Physician-in-Chief, László Dobszay, M.D., Associate Professor of Pediatrics at the University of Szeged, Hungary.

1. Halban: Zentralbl. f. Gynäk. **28**:1270, 1904.

of the umbilical cord or in the blood and urine of the newborn infant (Philipp;[2] Neumann and Péter[4]). The height of the hormone level and the fact that great quantities of estrogen can also be found in a newborn boy are evidence in favor of the maternal origin of these hormones. With the findings just cited, the possibility of diaplacental passage of hormones was proved, and Halban's theory, in consequence, seems much more probable.

Until now, evidence has been lacking as to whether heterologous hormones passively entering an organism could really produce such effects. I have been able to prove experimentally that they can.

In the course of experiments I came to two conclusions: 1. The limits given by Halban in defining the hormonal reactions of pregnancy must be materially enlarged to include as yet unknown or otherwise classified neonatal phenomena besides his original two, the physiologic

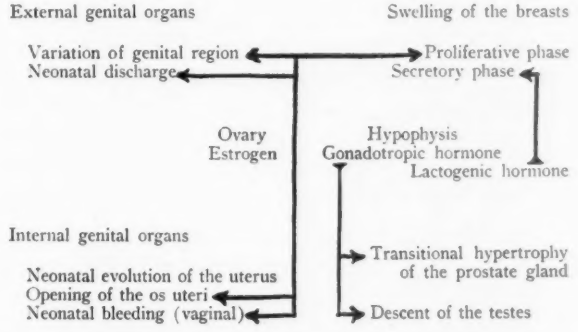

Fig. 1.—Schematic representation of the hormonal reactions of pregnancy.

mastitis and the physiologic vaginal bleeding of newborn infants. According to my investigations (fig. 1), variation of the genital environment in a newborn infant, physiologic neonatal discharge, neonatal evolution of the uterus and the opening of the os uteri in the neonatal period should be included in this classification. 2. Since I succeeded in making these reactions come about in an artificial way, not only could I thus prove, in a general way, their hormonal origin, but I could identify the hormonal factors that take part in causing these phenomena.

CHANGE IN THE GENITAL ENVIRONMENT

The genital picture is characterized both by the floral composition of the external genital organs and by the reaction of the vaginal secre-

2. Philipp, E.: Zentralbl. f. Gynäk. **53**:2386, 1929.
3. Footnote deleted by author.
4. Neumann, H. O., and Péter, F.: Ztschr. f. Kinderh. **52**:361, 1932.

tion. In this respect there is an essential difference between the neonatal period and the remaining period of infancy. It is known that the vaginal bacterial flora of children is of indefinite composition, being mostly cocci (Soeken;[5] Dychno and Derčinskij[6]). The reaction of the vaginal secretion is either slightly basic or neutral; very rarely it is slightly acid (Soeken;[5] Zwolinszky and Truszkowszky; Heurlin;[7] Lahm[8]). The composition of the bacterial flora is apparently entirely dependent on external factors, such as the bacterial content of surrounding organs and accidental pollution. On the contrary, soon after birth, a characteristic bacterial flora establishes itself in the vagina; this, after some transitionary phases of evolution, is exactly the same as the Döderlein vaginal flora present in adults (Menge;[9] Döderlein;[10] Schweitzer;[11] Smoródinzew and Tschumakowa;[12] Jötten;[13] Solomon[14]). By numerous periodic examinations of secretion, my associate and I (Dobszay and Hollósi[15]) have shown that the course of evolution of this flora is absolutely regular: The vagina is free of bacteria till a few hours after birth; then appear some gram-positive or gram-negative cocci of different sizes, with perhaps staphylococci or short-chained streptococci, in addition to gram-negative rods and Bacillus bifidus or Bacillus bipolaris. On the second day a luxuriant growth of mixed bacteria, mostly cocci, is present. Later some Döderlein bacilli enter; these become more numerous, till, on the fourth to the sixth day, they invade the entire field. Their sovereignty, however, lasts only two or three days. Soon deterioration of this flora begins, and again various microorganisms appear, till, approximately on the fourteenth day, the Döderlein flora vanishes entirely and its place is occupied by the micrococci usually found during childhood. According to my tests, concomitantly with the progression of the Döderlein flora, the vagina becomes strongly

5. Soeken, G.: Ztschr. f. Kinderh. **40**:727, 1926; **47**:27, 1929; Arch. f. Kinderh. **88**:194, 1929.

6. Dychno, M. A., and Derčinskij, A.: Arch. f. Gynäk. **142**:551, 1930.

7. af Heurlin, M.: Bakteriologische Untersuchungen der Genitalsekrete, der nichtschwangeren und nichtpuerperalen Frau vom Kindes- bis ins Greisenalter unter physiologischen und gynäkologisch-pathologischen Verhältnissen, Berlin, S. Karger, 1914.

8. Lahm, W.: Die pathologisch-anatomischen Grundlagen der Frauenkrankheiten, Dresden, T. Steinkopff, 1923.

9. Menge, C.: Zentralbl. f. Gynäk. **19**:796, 1895.

10. Döderlein, A.: München. med. Wchnschr. **42**:295, 1895; Centralbl. f. Gynäk. **18**:10 and 779, 1894; Arch. f. Gynäk. **31**:412, 1887.

11. Schweitzer, B.: Zentralbl. f. Gynäk. **43**:641, 1919.

12. Smoródinzew and Tschumakowa, abstracted, Zentralbl. f. Kinderh. **23**:794, 1929.

13. Jötten, K. W.: Arch. f. Hyg. **94**:174, 1924.

14. Salomon, R.: Klin. Wchnschr. **3**:1324, 1924.

15. Dobszay, L., and Hollósi, K.: Ztschr. f. Kinderh. **57**:133, 1935.

acidic and after the disappearance of this flora again becomes neutral. In my investigations the Döderlein flora evolved in only 80 per cent of the cases, while in 20 per cent it failed to develop. The regularity of the floral changes and the very fact that it fails to appear in one fifth of the cases bring to one's mind the question: On what does the evolution of the Döderlein flora depend? What factors bring about this peculiar change?

My investigations show that floral evolution, contrary to present day ideas, does not depend on contact with the maternal Döderlein flora during delivery; for in spite of plentiful contact or even direct experimental introduction, evolution fails to occur if suitable conditions for its habitat are lacking in the newborn child. Again, evolution occurs even if contact is meager or is excluded (e. g., through delivery by cesarean section or under sterile conditions), if suitable internal conditions insure it.

What are these conditions?

The development of the Döderlein flora and the acidity of the vaginal secretion closely coincide in time and appear with regularity; this fact shows that chemical factors play a part. However, in the course of my experiments I found that though under certain circumstances there was no difficulty in insuring the acid vaginal reaction usual in connection with the Döderlein flora, this reaction alone was not enough to bring about its growth. I had to come to the conclusion that much more profound histochemical changes provide the habitat of the Döderlein flora, changes that one cannot produce merely through the aforementioned external factors (i. e., by acidifying the vaginal secretion).

What then is the ultimate cause of these changes of the genital region in the neonatal period?

It is known that the closest harmony in time exists between the appearance or disappearance of the Döderlein flora and the continuance or discontinuance of the functioning of the sex hormone system of the woman (Schröder;[16] Mathes;[17] Lehmann;[18] Schwab;[19] Heurlin;[7] Gräfenberg;[20] Lahm;[8] Cruickshank and Sharman;[21] Loeser[22]). It

16. Schröder, R.: Lehrbuch der Gynäkologie für Studierende und Aerzte, Leipzig, F. C. W. Vogel, 1922.

17. Mathes, P., cited by von Jaschke, R. T.: Die normale und pathologische Genital-flora und das Fluorproblem, in Halban, J., and Seitz, L.: Biologie und Pathologie des Weibes: Ein Handbuch der Frauenheilkunde und Geburtshilfe, Berlin, Urban & Schwarzenberg, 1924.

18. Lehmann, F.: Zentralbl. f. Gynäk. **45**:647, 1921.

19. Schwab: Ztschr. f. Geburtsh. u. Gynäk. **89**:510, 1926.

20. Gräfenberg: Arch. f. Gynäk. **120**:120, 1923.

21. Cruickshank, R., and Sharman, A.: J. Obst. & Gynaec. Brit. Emp. **41**:190, 1934.

22. Loeser, A.: Med. Klin. **21**:1237, 1925.

was therefore justifiable to search for the role of hormonal factors of the histochemical conditions in the evolution of the flora of newborn infants. I sought for estrogenic methods to bring about artificially the establishment and development of Döderlein flora in subjects whose vaginal setting is otherwise unsuited to this flora—for example, in older infants, in whose vaginas occur the mixed coccus flora, the flora typical of childhood, together with basic reactions; in other words, in an environment where, according to my experiments, directly implanted Döderlein bacilli perish.

In a carefully conducted series of experiments (table) which thoroughly covered the subject (the details of which must be omitted for the sake of brevity), I determined first of all that infants receive estrogen without any ill effects in unbelievably large doses. Furthermore, I came to the conclusion that the gonadotropic factors of the anterior lobe of the hypophysis do not affect the genital region in any way; moreover, no favorable environment can be obtained for the Döderlein flora with small doses of estrogen. Colonies of Döderlein bacilli introduced into the vaginas of infants who had been treated as just mentioned failed to thrive and perished without exception within forty-eight hours after inoculation.

Next I tried extremely large doses of estrogen.[22a] From 100,000 to 150,000 units, divided into four or five doses, was administered within twelve days. Results were astounding. Immediately after the second injection appreciable swelling and redness appeared both on the external genital organs and on the wall of the vagina. Now I inoculated Döderlein bacilli. Next day the surface of the vagina and vulva was covered with a plentiful thin milky discharge; the pus contained great numbers of giant epithelial cells which stained well. At this time not the least sign of vaginal bacteria was present, although the discharge continuously increased and became thicker and more yellowish and the number of epithelial cells materially increased. On the fifth day numerous gram-positive vaginal bacilli suddenly appeared and in a short time overflowed to the surface, so that on the sixth or seventh day a perfectly evolved Döderlein flora was present, which indicated the highest degree of vaginal cleanliness.

The flora survived in its original composition for about seven days after I stopped giving injections of the estrogen; then gradually it disintegrated and within the next six or seven days gave way to the mixed coccic flora of childhood. The reaction of the vaginal discharge during the development of the flora was decidedly acid, the p_H being 4.6 to 4.4.

22a. The estrogenic substances administered were estrone (3-hydroxy-17-keto-1,3,5-estratriene) and estradiol benzoate (3-benzoate-17-hydroxy-1,3,5-estratriene).

The inoculated colonies derived from a strongly acidophilic culture of Bacillus vaginalis ordinarius vulgaris retained both their morphologic and cultural characteristics even after passage through human beings and could be cultivated easily from the infant's vagina either on dextrose agar or in lactic acid-dextrose broth. In several cases a perfect Döderlein flora appeared without previous inoculation of the bacilli; it is evident that in these cases a few microbes got into the vagina from the outside. This furthermore proves that the artificial transformation of the histochemical reaction was so thorough that even the slightest contact with Döderlein bacilli was enough to permit evolution of a perfect and complete flora.

Fig. 2.—Vaginal epithelium of an infant treated with an estrogenic substance.

After these successful experiments the question arose: What histochemical changes took place through the action of the estrogen so that the environment became suitable for the growth of the Döderlein flora?

It is known that the adult vaginal epithelium contains great quantities of glycogen. Close correlation exists between the abundance of glycogen and the purity of the Döderlein flora (Stephan;[23] Niederehe; Gräfenberg;[20] Cruickshank and Sharman;[21] Kessler and Lehmann;[24] Schwab;[19] Geller[25]). Similarly, the vaginal epithelium of the newborn

23. Stephan, S.: Zentralbl. f. Gynäk. **45**:1565, 1921.
24. Kessler, R., and Lehmann, F.: Arch. f. Gynäk. **133**:791, 1928.
25. Geller, F. C.: Arch. f. Gynäk. **125**:408 and 444, 1925.

infant also contains plenty of glycogen during the development of the Döderlein flora (Cruickshank and Sharman;[21] Širjaeva-Rodionova;[26] Gragert[27]). On the contrary, during the latter part of childhood, till the onset of puberty, glycogen cannot be found in the vaginal epithelium. Owing to this apparent correlation, I continued my investigations to ascertain whether the presence of glycogen can be demonstrated in the vaginal epithelium of infants treated with estrogen. In a series of histologic examinations, carried out according to Best's method, I was able to conclude, as I had expected, that plentiful glycogen appears in the epithelium of the vagina of a newborn infant through the action of estrogen.

That often argued but hitherto unsettled question as to whether glycogenolysis, that is, the acidity is due to the action of Döderlein bacilli or, without their influence, is due to the action of tissue ferments alone, was easily cleared up by my experiments. Here the inoculation of Döderlein bacilli could be controlled according to need or preference. I was able to examine the glycogenolysis after the development of the action of the estrogen but before the appearance of the Döderlein flora, an experimental state which cannot be created under normal conditions, i. e., in the adult.

Throughout my experiment I made regular ferment determinations according to Wohlgemuth's method; for the comparison of amylase values, I used 100 mg. of vaginal discharge as the basis of computation (table). Sometimes the vaginal discharge had some slightly glycogenolytic property even before the estrogenic treatments, but only in case the newborn child had a discharge before the treatments, that is, if it was due to increased desquamation, increased destruction of cells continued. When there was no discharge the Wohlgemuth test always gave negative results.

However, amylase appeared as a result of doses of estrogen in the vagina of every infant treated; moreover, the amylase content increased simultaneously with the increase of the discharge, so that at the peak of the hormonal reaction, approximately on the sixth day, the diastatic power reached a high value ($D\frac{37}{24}$: 120.5—2,000 mg.).

One must accept as an additional effect of the estrogen that change taking place in the vaginal epithelial structure which results in increased cellular destruction, this in turn increasing the ferment content of the discharge.

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26. Širjaeva-Rodionova, E., abstracted, Ber. ü. d. ges. Gynäk. u. Geburtsh. **16**: 109, 1928.

27. Gragert, O.: Arch. f. Gynäk. **128**:43, 1926.

Synchronously with the appearance of the glycolytic ferment, the vaginal discharge begins to acidify: Its reaction changes from neutral or slightly basic to strongly acid. According to my investigations this acidification is due to production of lactic acid. The titrable acidity gradually increases till it reaches its maximum value of 0.88 to 264 cc.

Summary of Experiments

Subject	Day of Experiment	Amount of Estrogenic Substance Injected (in 1,000 Units)	Copiousness of Flow	Quantity of Glycogen	D $37°^{24h}$ (in 100 Mg.)	Titrable Acidity	p_H
F. J.	Before the experiment		+	0†	6.5	0†	7.40
	1-2	25-25	+	—	—	—	—
	3	—	++	0	16.6	0.75	6.80
	4-5	25-25	+++	—	—	—	—
	6	—	+++	+	80.6	0.88	5.64
	Appearance of Döderlein bacilli						
	7-8	—	+++	—	—	—	—
	10	—	+++	++	120.2	3.00	4.92
	14	—	++	0	—	—	—
	21	—	0†	0	0	—	7.20
B. G.	Before the experiment		0	0	0	0	7.20
	1-2	25-25	—	—	—	—	—
	3	—	0	++	19.2	0.81	6.50
	4-5	25-25	++	—	—	—	—
	6	—	+++	++	330.3	1.13	5.20
	Appearance of Döderlein bacilli						
	7-9	—	+++	—	—	—	—
	10	—	+++	+++	340.5	3.51	4.68
	14	—	++	+	—	—	—
	21	—	0	0	0	0	7.10
G. A.	Before the experiment		0	0	0	0	7.30
	1-2	25-25	+	—	—	—	—
	3-4	25-25	+	+?	20.0	0.60	6.80
	5	—	+++	+++	400.0	0.60	6.80
	7	—	+++	++	1200.0	2.64	5.80
	Appearance of Döderlein bacilli						
	9	—	+++	++	1800.0	2.93	5.80
	12	—	+++	+	2500.0	3.46	4.90
	16	—	++	+	166.0	0.80	5.60
	18	—	+	0	83.0	0.20	6.00
	21	—	+	0	20.0	0	7.20
K. J.	Before the experiment		0	0	0	0	7.20
	1-2	25-25	—	—	—	—	—
	3-4	25-25	++	0	26.0	0.62	7.00
	5	—	++	+	48.0	0.62	6.80
	7	—	+++	+++	133.0	2.41	6.20
	Appearance of Döderlein bacilli						
	9	—	+	+?	1200.0	2.70	5.20
	12	—	++	0	1250.0	2.60	4.50
	16	—	+	0	120.0	0.86	5.00
	18	—	+	0	40.0	0.26	5.80
	21	—	0	0	0	0	7.30

* Diastatic power in twenty-four hours at 37 C.
† The symbol "0" indicates that results were inconclusive or that the quantity of material was not sufficient for the test.

based on 100 mg. of discharge and hundredth-normal sodium hydroxide. Parallel with this the value of the hydrogen ion concentration moves from a point between 7.2 and 7.4 to one between 6.2 and 5.2.

I wish to emphasize that the change of the chemical environment is due entirely to the action of tissue ferments and that it begins long before the introduction of the Döderlein flora.

Acidity perceptibly increases after the introduction, or rather after the multiplication, of Döderlein bacilli. It is evident that the Döderlein flora itself joins in the production of acid; however, probably it does this not directly but by taking over the carbohydrate disintegration begun by the ferment and continuing the breaking down into still smaller molecules.

The relation existing between the environmental changes just outlined and the action of the estrogen appears proved by the fact that after this substance has passed from the body, that is, two weeks after the last dose, the vaginal discharge abates and then stops, the glycolytic ferment disappears, the quantity of titrable acid drops to zero and the hydrogen ion concentration is pushed back to between 7.2 and 7.4.

NEONATAL DISCHARGE

The series of experiments just presented indicated in addition the origin and classification of another physiologic phenomenon of the neonatal period: the neonatal discharge.

On examination of the external genital organs of a newborn girl the observer is struck by the swollen and congested appearance of the vulva, even immediately after birth. The congestion appears also on the clitoris, on the labia minora and, as endoscopic examination proves, on the mucous lining of the vagina. The swelling and congestion continually increase, reaching their maximum on the fourth to the sixth day. At the same time a specific discharge starts to flow, and the resulting thin, milklike, later thicker and more yellowish secretion covers the entire surface of the vagina.

Epstein [28] described this phenomenon and named it vulvovaginitis desquamativa; he thought it to be physiologic. He explained it as a part phenomenon of the general desquamation of newborn infants. The name and explanation attained universal recognition in the literature.

Although (owing to control experiments) I consider as correct Epstein's clinical description of this phenomenon, I doubt his theory as to the origin of the discharge. No chronologic correlation could be shown between the qualitative and quantitative appearance or the change of the secretion and desquamation. However, there is a striking correspondence between the Döderlein flora and the discharge, in that the development of the Döderlein flora and the amount of discharge reach their maximum exactly at the same time. On the other hand, a negligible amount of discharge or none appeared when the Döderlein flora could not get a foothold.

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28. Epstein: Arch. f. Dermat. u. Syph. (supp.) **23**:3, 1891.

I was aware of the fact that the common origin of the discharge and of the genital change could be proved only if it was possible to reproduce both artificially under similar conditions. My efforts toward this end were for a long time unsuccessful, but at last I was able to find the previously described means for the artificial creation of the physiologic genital environment.

Then I observed that, besides those bacterial and chemical changes brought about on the genital organs of older infants by 100,000 to 150,000 units of estrogen, clinical symptoms of striking character were to be noted. Soon after the second injection of estrogen (a total of 40,000 units) definite swelling and congestion appeared on the mucosa of the introitus and of the vagina. Following this, a discharge started, continually increasing till at the peak of the reaction (approximately on the fifth or sixth day), at the time of the fullest development of the Döderlein flora, a decided and copious flow could be observed. Production of the discharge lasted six to eight days, then decreased and twelve to fourteen days after the discontinuation of the injections disappeared without leaving any trace. The course, quality and cytologic peculiarities of the discharge were exactly similar to those of the discharge of newborn infants.

SEAL OF THE OS UTERI

Changes as interesting as those just described can be observed during the neonatal period in the internal genital organs of infants. I was most interested in the behavior of the seal of the os uteri. This question is of great importance on account of the pathologic changes of gonorrhea in children. As is known, the os uteri is closed during childhood till the onset of puberty, and it is owing to this fact that an inflammatory process of the vagina seldom extends into the cavity of the uterus.

The question is: What constitutes the seal of the os uteri? According to some it is cellular adhesion of the cervical canal, while according to others it is mucous comedo filling the cervical canal. It is certain that the seal lasts only till puberty and can be considered destroyed with the first menstruation.

I was interested from a practical point of view in the resistance of the seal to mechanical force acting through the vagina. I made experiments on fresh preparations of vagina and uterus taken from infants and older children who had died of various diseases. The experiments were carried on with a specially constructed apparatus with which one could compress air or water through the lumen of the vagina according to need and at the same time measure the attained pressure on an atmospheric or a mercury manometer. It became apparent that during

infancy and later childhood (before puberty) neither air nor liquid can be forced through the os uteri even under great pressure (1 or 2 atmospheres), even if so much of the uterus is cut away that only about 2 or 3 mm. of the cervix alone remains. To decide whether this extraordinarily resistant seal is due to cellular adhesion of the cervical canal, to mucous comedo or to elastic contraction of the cervical canal, I performed experiments with pressure in the following way: I cut away the uterus almost completely and then, while it was still under compression from the vaginal side, I introduced hollow probes from the proximal part of the cervical canal into the vagina; immediately a flow of air or liquid passed through. This operation should have removed the seal of the os uteri if it is caused by either cellular adhesion or mucous comedo. It did not, however, for after the probe was withdrawn the os uteri contracted elastically, and the seal again worked perfectly. I could repeat the probing any number of times, even dilating the canal to a certain extent, but the seal still remained intact.

Therefore, the os uteri in childhood is elastically closed to such an extent that even extraordinarily great pressures acting through the lumen of the vagina cannot break the seal.

I observed that in the case of preparations obtained from fully matured, but only from fully matured, newborn infants the experiments gave entirely different results. These were of decisive importance in finding the regulating mechanism of the seal of the os uteri. I found that in such cases it was possible to force air or liquid through the cervical canal even with extremely low (10 to 20 mm. of mercury) pressures. During the neonatal period the os uteri is open, and according to my experimental observations this state exists till the third week of life. At that time it closes and remains closed till the beginning of puberal evolution.

What is the cause of this phenomenon? The very fact that the os uteri opens in connection with puberal evolution brings hormonal action to the fore in the mind of the observer. I can substantiate this hypothesis with exact data. I observed 3 infants who, on account of gonorrhea, had received treatment with estrogen as devised by Lewis; however, they died of intercurrent diseases during therapy. In these infants the os uteri was found to be open, a condition contrary to that found in infants of similar age. At the same time I found that their uteri were materially larger and softer than usual, as in newborn infants, whose uteri, as is known, enlarge to from 35 to 40 mm. in length and to 4 Gm. in weight, diminishing after about three or four weeks to 25 mm. and 2.5 Gm., respectively.

This observation throws light on the origin of two physiologic neonatal phenomena: the evolution of the uterus of a newborn infant and the temporary opening of the seal of the os uteri. According to

what has been said, both can be traced to the action of the estrogenic hormone or, to be exact, to the estrogenic hormone of maternal origin.

NEONATAL MASTITIS

Finally, I should like to acquaint the reader with my experiments concerning the origin of physiologic neonatal mastitis, considered by Halban to be a typical reaction of pregnancy.

I was led to examine the matter by an accidental observation. When, for the purpose of artificially creating physiologic changes in the genital region, I had given an estrogenic substance to older children, after the injection of a certain amount (approximately 100,000 to 150,000 units) definite swelling of the breast occurred in both boys and girls (fig. 3); this grew day by day till it presented the picture of neonatal swelling of the breast. However, I must point to one important difference between this swelling and physiologic mastitis: viz., that with the former phenomenon a secretion could never be noted, while it is a constant companion of the latter.

Fig. 3.—Swelling of the breast after treatment with an estrogenic substance.

On the basis of this experiment (strengthened by observations of others, who had different points of view) it could be ascertained that the proliferative phase of development of the breast, but only the proliferative phase, can be brought about by doses of an estrogenic substance.

The artificial reproduction of the secretory phase was yet to be achieved. Studies on animals (undertaken mainly by American authors: Riddle, Bates and Dykshorn;[29] Lyons and Catchpole;[30] and others) for the artificial starting of secretion of milk and clinical experience in treating women who secreted milk scantily brought my attention to the lactogenic hormone, prolactin, which was discovered by Stricker and Grueter[31] in 1929 and since then has been extracted in a pure state from the anterior lobe of the hypophysis.

29. Riddle, O.; Bates, R. W., and Dykshorn, S. W.: Am. J. Physiol. **105**:191, 1933.

30. Lyons, W. R., and Catchpole, H. R.: Proc. Soc. Exper. Biol. & Med. **31**: 299, 1933.

31. Stricker, P., and Grueter, F.: Presse méd. **37**:1268, 1929.

I carried out further studies, giving on three successive days a daily dose of 10 Gm. of the lactogenic factor to those infants in whom I produced the proliferative phase of development of the breast with doses of an estrogenic substance.

The results were fully up to expectation, for soon signs of secretion appeared, and it was possible to press from the breasts secretion containing whitish yellow colostral bodies in great quantity.

Control experiments determined that swelling of the breasts and secretion cannot be brought about by the lactation-stimulating substance alone (i. e., without previous treatment with estrogenic substance), nor can it be produced if the preliminary treatment was done with an extract of corpus luteum. Swelling of the breasts and secretion of milk disappeared about two to four weeks after the drug was discontinued, without leaving any trace.

Important conclusions can be drawn from my studies as to the origin of natural secretion of milk, on the one hand, and of physiologic neonatal mastitis, on the other. Without doubt, in the appearance of the latter estrogen and the lactation-stimulating hormone of the hypophysis (both of maternal origin) play the dominant role.

SUMMARY AND CONCLUSIONS

I succeeded in bringing about artificial adherence and evolution of the Döderlein flora in human beings, for the first time, by means of estrogen, thereby making possible the experimental study of the physiologic evolution of the genital region.

I have shown that it is the estrogenic hormone that stands in the key position of regulation of these organs. By its action, first addition of glycogen and then increased desquamation of the mucous membrane occur. A glycolytic ferment that is freed through the disintegration of desquamated epithelial cells causes acidity; thus is prepared the bed for Döderlein bacilli, or rather for their cooperation in further production of acid.

My artificially produced change of the genital picture was similar in every aspect to that which can be observed in newborn infants. There can be no doubt that the latter (i. e., the natural change) comes about similarly by the action of the estrogenic hormone of maternal origin and as such belongs among the hormonal reactions of pregnancy.

The estrogenic hormone of maternal origin physiologically produces the discharge from the vaginas of newborn infants; therefore, it too must be considered as a hormonal reaction of pregnancy. Thus Epstein's explanation of this phenomenon and the name he gave it are proved to be untrue and hence unacceptable.

I have shown that the estrogenic hormone is the regulating mechanism of the seal of the os uteri; this same substance brings about those

macromorphologic changes of the uterus that are observed during the neonatal period. Therefore the two neonatal phenomena, namely, the transitory opening of the os uteri and the evolution of the uterus of a newborn infant, also belong among the hormonal reactions of pregnancy.

For the first time in human beings, successful efforts have been made to start artificial lactation (production of milk) in entirely immature fundamental breast tissue in subjects in which the proliferative development also had an artificial origin. The phenomenon thus demonstrated completely coincides with the physiologic neonatal mastitis; hence the results of my investigations not only strengthen Halban's explanation of this phenomenon in a general way but prove that the follicle-stimulating and the lactation-stimulating hormones of maternal origin play a part in its origin.

The clarification of the origin of these varied, yet genetically closely allied, phenomena materially enlarges the circle of the hormonal reactions of pregnancy without, however, completing it.[32]

A further study of the problem would seem advisable, especially in two connections:

1. It would prove fruitful from the angle of gynecologic physiology, since the processes described are similar to and in certain instances exactly like the physiologic processes that can be observed in women. These phenomena ought to be considered as biologic models, since they permit numerous observations for which adults are unsatisfactory subjects.

2. As for the pediatric point of view, more exactly that of neonatal physiology, the study of these problems involves far more than the instances just mentioned. Although the enormous hormonal revolution associated with pregnancy brings to the fore the "sex hormone" complexes of both mother and child, still it cannot be denied that a similar investigation of other hormone complexes would put in a different light some of the physiologic phenomena of newborn infants. May I point to just one obvious possibility as an example: the peculiarities of the salt and water metabolism of the newborn. It seems not impossible that one may find data in connection with it which would increase the number of known hormonal reactions of pregnancy, if this term is used in the widest sense.

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32. According to studies which I have not as yet completed, the often noticed transitory hypertrophy of the prostate gland in newborn boys also belongs essentially to the hormonal reactions of pregnancy, as it seems to come about through the action of maternal gonadotropic hormones. In a wider sense, descent of the testis is one of the hormonal reactions of pregnancy.

ACTIVE IMMUNIZATION AGAINST WHOOPING COUGH WITH VARIOUS SPECIFIC VACCINES

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For about twenty-five years, ever since the earliest attempts to prevent whooping cough by the use of specific vaccines, there have been conflicting reports [1] as to their value. In efforts to make the vaccine more effective, changes were made in the method of preparation [2] and in the dose.[3] The trend has been toward the use of increasingly larger doses of vaccines prepared from virulent or phase I strains.[2b] The dose has been increased since 1912 from less than a billion bacilli [4] to 80 and 100 billion bacilli [1c] and more.[5] As for the method of preparation, Sauer has placed a great deal of emphasis on the necessity of employing recently isolated strains in preference to stock strains, even though their antigenicity has been maintained under suitable cultural conditions.[6] In addition, some investigators [7] have emphasized the

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From the Bureau of Laboratories of the Department of Health of New York City.

1. (*a*) Luttinger, P.: Pertussis Vaccine: Its Value as a Curative and Prophylactic Agent in Whooping Cough, J. A. M. A. **68**:1461 (May 19) 1917. (*b*) von Sholly, A. I.; Blum, J., and Smith, L.: Therapeutic Value of Pertussis Vaccine in Whooping Cough, ibid. **68**:1451 (May 19) 1917. (*c*) Sauer, L.: Whooping Cough: A Study in Immunization, ibid. **100**:239 (Jan. 28) 1933. (*d*) Siegel, M., and Goldberger, E. W.: Active Immunization of Tuberculous Children Against Whooping Cough with Sauer's Vaccine, ibid. **109**:1088 (Oct. 2) 1937.

2. (*a*) Bordet, J., and Gengou, O.: Le microbe de la coqueluche, Ann. Inst. Pasteur **20**:731, 1906. (*b*) Mishulow, L.; Mowry, I. W., and Scott, E. B.: Pertussis Toxic Filtrates and Toxin-Vaccines, J. Immunol. **19**:227, 1930. (*c*) Leslie, P. H., and Gardner, A. D.: The Phases of Haemophilus Pertussis, J. Hyg. **31**:423, 1931.

3. (*a*) Luttinger.[1a] (*b*) Sauer.[1c] (*c*) Madsen, T.: Vaccination Against Whooping Cough, J. A. M. A. **101**:187 (July 15) 1933.

4. Zahorsky, J.: The Bacterin Treatment of Pertussis, Interstate M. J. **19**:844, 1912.

5. Daugherty-Denmark, L.: Studies in Whooping Cough: Diagnosis and Immunization, Am. J. Dis. Child. **52**:587 (Sept.) 1936.

6. (*a*) Mishulow, L.; Mowry, I. W., and Orange, R.: A Comparative Study of Agglutinin Response After Pertussis Vaccination with the Sauer Vaccine and with a Toxin-Vaccine and in Untreated Clinical Pertussis, J. Pediat. **9**:492, 1936. (*b*) Shibley, G. S., and Hoelscher, H.: Studies on Whooping Cough: Type-Specific (S) and Dissociation (R) Forms of Haemophilus Pertussis, J. Exper. Med. **60**:403, 1934.

7. Sauer.[1c] Mishulow, Mowry and Orange.[6a]

immunizing value of toxic substances in cultures grown under well defined conditions and have therefore urged the use of unwashed vaccines in preference to washed vaccines.

It was the purpose of my associates and myself to subject these claims to clinical experimentation by employing various whooping cough vaccines under adequate control conditions. The study was designed originally by Dr. William H. Park to verify Sauer's early claims that 80 billion bacilli of his vaccine would afford complete protection against whooping cough and to compare the effectiveness of Sauer's vaccine prepared from recently isolated strains with several vaccines prepared from stock strains. It was also planned to evaluate the influence of the dose and of the intradermal route in active immunization against whooping cough.[8]

For these purposes, we employed Sauer's commercial vaccine prepared by Eli Lilly & Company and by Parke, Davis & Company, the vaccine of the New York Department of Health made from a virulent stock strain six to eighteen months old by the method developed by Miss Mishulow of the Bureau of Laboratories, and a vaccine prepared by Dr. Povitzky of the Bureau of Laboratories from a strain isolated in 1925. These were administered subcutaneously in doses of 80 billion bacilli. In addition, three commercial vaccines (treated with a solution of formaldehyde, heat-killed and toxoid) prepared by Lederle Laboratories, Inc., from stock strains, were employed subcutaneously in doses of 30 billion bacilli, as recommended by the company. The value of the intradermal inoculation of part of the vaccine was tested in a group of children who were given 12 billion bacilli of the vaccine of the New York Department of Health intradermally and 68 billion bacilli subcutaneously. This same vaccine was given subcutaneously to another group in the small dose of 7½ billion bacilli.

The vaccines were given to children living in Brooklyn who were under the age of 6 years and who had no previous history of whooping cough or of vaccination against whooping cough. They were sent to the clinic at the Prospect Board of Health Station of the New York Department of Health by the various baby health stations in Brooklyn or by friends and neighbors who knew that whooping cough vaccine was available at our clinic. All who applied for the vaccine were inoculated. Controls were not chosen from this group because all requested the vaccine. We chose as our controls unvaccinated children from the neighborhoods of the vaccinated children. They were under the age of 6 years and had no previous history of whooping cough. Wherever possible, playmates or siblings of vaccinated children were chosen. An effort was made to have approximately as many controls in each district as there were vaccinated children.

The vaccinations were begun on July 29, 1935, and were continued for nine months, until April 29, 1936. During this period 1,324 children were inoculated. A total of 1,096 children (82.8 per cent) returned for the full course of three inoculations (full dose), while 228 children (17.2 per cent) received only one or two inoculations (partial dose). About two thirds of the vaccinated children were inoculated during the first three months of the study (August, September and October 1935). This was during the latter part of the whooping cough

8. Dr. Camille Kereszturi helped to plan and organize the work when it was begun.

season, when the mothers were apprehensive and were therefore eager to come for the vaccine. Afterward the number of children applying for the vaccine was reduced considerably, and as a result only about one third of the vaccinated children were inoculated during the six months from November 1935 to April 1936.

As the children applied for the vaccine, they were assigned in consecutive order to one of the eight groups in the study. This was continued for four months, until Nov. 30, 1935. After that we added no new children to the four groups who received doses of 30 billion bacilli or less because our results seemed to indicate early in the study that such doses were of little, if any, value in the prevention of whooping cough. Therefore, we limited the vaccinations after November 30 to the four groups who received the larger doses (80 billion bacilli).

The follow-up study of the vaccinated and control children was carried out by means of visits to the homes. These were conducted by WPA investigators, who were chosen from a group of pharmacists and trained by us for this work. They inquired about illnesses and exposure to whooping cough. Their findings were reported on standard forms designed to indicate the details of the exposure or illness. A circumscribed area containing an average of 200 children was assigned to each investigator and retained by him throughout the entire period of the follow-up study. A visit to each home was made at least once a month. In case of illness or exposure to whooping cough, a visit was made once a week until a final decision was reached as to the nature of the illness or the outcome of the exposure. I reviewed the investigators' reports periodically, and every child suspected of having whooping cough was examined by a physician from the Department of Health for clinical evidence of the disease. No provisions were made for blood counts or for cough plate cultures.

The diagnosis of whooping cough was made only after the whoop appeared. It was confirmed in each case by a physician from the Department of Health. Cases of a cough unaccompanied by the characteristic paroxysms were not tabulated in the analyses of occurrences. However, if in such cases there had been familial or extrafamilial exposure to whooping cough, the condition was considered as possible whooping cough and was classified under the heading "cough without whoop" in an analysis of the effects of exposure (table 3).

Those cases in which characteristic whooping cough developed during the period of vaccination or less than one month after the completion of the vaccination were excluded from the series because it was felt that exposure probably occurred before the maximum protective effect of the vaccine had been reached.

The control children were considered in the same manner as those who were vaccinated. Those in whom whooping cough developed within the first month of the follow-up study were excluded from the series.

The study terminated on June 30, 1937, from fourteen to twenty-three months after vaccination. During this period we observed 1,270 (95.9 per cent) of the 1,324 vaccinated children and 1,016 (92.1 per cent) of the 1,103 control children, a total of 2,292 children. About 96 per cent of these children lived in Brooklyn throughout the period of study and were therefore revisited monthly in their homes by investigators. The remaining 4 per cent moved from Brooklyn and were followed by mail at monthly intervals.

The age distribution was fairly similar for each of the various vaccinated groups. About 87 per cent of the vaccinated children were from 1 to 4 years old, and about 7 per cent were under 1 year of age. Among the controls, approximately 78 per cent were from 1 to 4 years old and about 15 per cent were under 1 year of of age.

RESULTS

There were 46 (3.6 per cent) occurrences of characteristic whooping cough among the vaccinated children, as compared with 43 (4.2 per cent) among the controls. Of the 46 vaccinated children, 35 (3.3 per cent) received the full dose of vaccine and 11 (5.2 per cent) received partial doses only (table 1).

The incidence of characteristic whooping cough among the various groups of children who were vaccinated with the full dose varied from

TABLE 1.—*Incidence of Characteristic Whooping Cough One Month or More After Completion of Vaccination*

Vaccine	Full Dose*						Partial Dose†				
			Incidence						Incidence		
	Dose in Billions of Bacilli	Number of Vaccinated Children	1 to 3 Mo. After Vaccination	4 Mo. or More After Vaccination	Total	Percentage	Dose in Billions of Bacilli	Number of Vaccinated Children	1 to 3 Mo. After Vaccination	4 Mo. or More After Vaccination	Total
Sauer's authorized commercial vaccine	80	154	..	..	0	0	20-50	27	1	..	1
Vaccine of New York Department of Health	80	140	..	..	0	0	20-50	36	..	..	..
Vaccine of New York Department of Health	80‡	148	1	3	4	2.7	20-50	26	1	1	2
Vaccine from strain isolated in 1925 by Povitzky	80	158	..	6	6	3.8	20-50	25	..	2	2
Lederle Laboratories, Inc.											
Vaccine treated with a solution of formaldehyde	30	121	3	3	6	4.9	5-15	28	..	1	1
Heat-killed vaccine	30	118	..	5	5	4.2	5-15	23	..	1	1
Toxoid vaccine	30	119	1	7	8	6.7	5-15	15	..	4	4
Vaccine of New York Department of Health	7½	101	1	5	6	5.9	1½-4½	21	..	..	..
Total (full dose)		1,059	6	29	35	3.3		211	2	9	11 (5.2%)
Controls		1,016	8	35	43	4.2					

* Full dose indicates that the full amount of vaccine was received in three doses.
† Partial dose indicates that only one or two of the three doses required to complete the vaccination were received.
‡ Approximately 12 billion bacilli were administered intradermally and 68 billion bacilli subcutaneously.

0 to 6.7 per cent, while the controls had an incidence of 4.2 per cent (table 1).

There were no occurrences of characteristic whooping cough in two groups, comprising a total of 294 children, who were inoculated subcutaneously with 80 billion bacilli of either Sauer's vaccine or the vaccine of the New York Department of Health (table 1). On the other hand, there were 4 cases (2.7 per cent) among those who received similar doses of the vaccine of the New York Department of Health, injected partly subcutaneously (68 billion bacilli) and partly intradermally (12 billion bacilli). Among those inoculated subcu-

taneously with 80 billion bacilli of the vaccine prepared by Dr. Povitzky from a very old stock strain, there were 6 (3.8 per cent) occurrences. The incidence of characteristic whooping cough in these four groups of children who were inoculated with 80 billion bacilli varied from 0 to 3.8 per cent. In each group it was less than that among the controls.

In each of the remaining four groups, in which the doses of 30 billion bacilli or 7½ billion bacilli were employed, there were from 5 to 8 cases of characteristic whooping cough (table 1). The attack rate varied from 4.2 per cent to 6.7 per cent. This was equal to or greater than that among the controls.

Those vaccinated with partial doses also had relatively more occurrences than the controls. Among these 211 children there were 11 occurrences, an incidence of 5.2 per cent (table 1).

TABLE 2.—*Comparison of Results in the Groups Inoculated with Eighty Billion Bacilli and Those Inoculated with Smaller Doses*

Dose	Children	Incidence of Characteristic Whooping Cough (One Month or More After Vaccination)	Percentage of Vaccinated Children
Vaccinated children			
80 billion bacilli	600	10	1.7
1½ to 50 billion bacilli*	670	36	5.4
Total	1,270	46	3.6
Controls	1,016	43	4.2

* Including 358 children inoculated with 30 billion bacilli, 101 children vaccinated with 7½ billion bacilli and 211 children inoculated with partial doses (table 1).

On the whole, therefore, those who received 80 billion bacilli did somewhat better than the controls, while the incidence among those who received smaller doses (50 billion bacilli or less) was slightly greater than that among the controls (table 2).

The age distribution of the children who contracted characteristic whooping cough was as follows:

Age in Years	Vaccinated Children	Control Children
0-1	1	6
1-2	12	11
2-3	13	7
3-4	11	5
4-5	6	8
5-6	3	6
	46	43

None of these children died.

An analysis of our data on exposure (table 3) indicates that in relatively few instances was exposure known to occur one month or more after vaccination. Exposures occurring before this period were not included in the tabulation because it was felt that they took place before the maximum protective effect of the vaccine had been reached.

There were 23 cases (1 per cent) of familial exposure, 10 of which were among the controls and 13 among the vaccinated children. Of the vaccinated children, 5 contracted characteristic whooping cough, 4 had a cough unaccompanied by a whoop, and 4 showed no effects. Of the control children, 8 had characteristic whooping cough, and 2 had no symptoms. In short, symptoms developed in most of the children with familial exposure, both those who were vaccinated and those

TABLE 3.—*Number of Known Exposures and Their Effects*

Type of Inoculation	Dose in Billions of Bacilli	Number of Vaccinated Children	Familial Exposures					Extrafamilial Exposures				
				Effects of Familial Exposures					Effects of Extrafamilial Exposures			
						Characteristic Whooping Cough					Characteristic Whooping Cough	
			Number of Exposures	None	Cough Without Whoop	1 to 3 Mo.* After Vaccination	4 Mo. or More* After Vaccination	Number of Exposures	None	Cough Without Whoop	1 to 3 Mo.* After Vaccination	4 Mo. or More* After Vaccination
Vaccine												
Sauer's authorized commercial vaccine	80	154	1	1	..	..	..	4	3	1	..	..
Vaccine of New York Department of Health	80	140	1	..	1	..	..	6	4	2	..	..
Vaccine of New York Department of Health	80†	148	2	1	1	..	..	10	7	..	1	2
Vaccine from strain isolated in 1925 by Povitzsky	80	158	..	..	..	..	..	9	2	3	..	4
Lederle Laboratories, Inc.												
Formaldehydized vaccine	30	121	3	1	1	..	1	11	3	1	1	1
Heat-killed vaccine	30	118	1	..	..	..	1	7	4	2	..	1
Toxoid vaccine	30	119	..	..	..	..	..	10	4	1	1	4
Vaccine of New York Department of Health	7½	101	..	..	..	..	..	4	3	..	..	1
Dose												
Full dose	..	1,059	8	3	3	0	2	61	35	10	3	13
Partial dose	1½-50	211	5	1	1	1	2	7	3	0	2	2
Full or partial dose	..	1,270	13	4	4	1	4	68	38	10	5	15
No inoculation	..	1,016	10	2	0	2	6	45	20	7	4	14

* The headings "1 to 3 months" and "4 months or more" refer to the interval between the completion of vaccination and the occurrence of whooping cough.

† Approximately 12 billion bacilli were inoculated intradermally and 68 billion bacilli subcutaneously.

who were controls. There were a few more cases of characteristic whooping cough among the controls than among the vaccinated children.

Extrafamilial exposure occurred in 113 cases (4.9 per cent). Sixty-eight of the exposed children were vaccinated, and 45 were controls. In this group we included those children who had been in daily contact with a playmate or neighbor with clinical symptoms of whooping cough. Casual, momentary contacts were excluded, because the likelihood of exposure was remote and because there was no way of determining

whether contact occurred during the infective period. We feel that even after careful selection data relative to extrafamilial exposure are not wholly reliable and may be highly misleading.

In 30 of the 68 vaccinated children who were considered to have had extrafamilial exposure symptoms of infection developed. Of these children, 20 had characteristic whooping cough, while 10 had a cough without a whoop. Of the 45 controls subjected to extrafamilial exposure, symptoms appeared in 25. Eighteen of these had characteristic whooping cough, and 7 had a cough unaccompanied by a whoop. There was therefore great similarity between the effects of extrafamilial exposure on the controls and the effects on the vaccinated children. The incidence of characteristic whooping cough was only slightly less among the vaccinated children than among the controls.

Since characteristic whooping cough did not occur among the 294 children vaccinated subcutaneously with 80 billion bacilli of Sauer's vaccine or the vaccine of the New York Department of Health, the data on exposure in this group are of particular interest. Only 1 (0.3 per cent) of the 294 children was exposed to whooping cough in the immediate family. No symptoms of infection developed in this child. Extrafamilial exposure was reported for 10 (3.4 per cent) children of this group. Three contracted a cough unaccompanied by a whoop, while the other 7 had no symptoms.

In general, symptoms developed almost as often among the vaccinated children after known exposure as among the control children. However, the incidence of characteristic whooping cough was somewhat smaller among the vaccinated children than among the controls.

The relatively small number of instances of known familial and extrafamilial exposure was to be anticipated from the low incidence of whooping cough among all the children in the series. A low rate of attack was also reported for New York as a whole for the year 1936.

We attempted to evaluate the severity of the disease among vaccinated children and controls. We found that we were unable to do this with any degree of accuracy because our data were obtained from parents, whose objectivity and basis for judgment in respect to whooping cough are faulty.[1b] Furthermore, it is well known that the disease can vary considerably not only among groups of children but also in the same child from day to day.[9] We therefore wish to caution against the unquestioned acceptance of impressions concerning the severity of whooping cough, particularly in children treated at home.

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9. Bamburger, P., and Merke, H.: Der Normalverlauf der Keuchhustenerkrankung als Maszstab zur Beurteilung von Heilversucken, Klin. Wchnschr. **14:** 1036, 1935. Miller, J. J., Jr., and Singer-Brooks, C.: The Variable Course of Pertussis, Am. J. Dis. Child. **53:**720 (March) 1937.

COMMENT

In evaluating the results of clinical trials, it is obviously essential to know the degree of exposure to which the children have been subjected. Unfortunately, in clinical trials in the general population the degree of exposure is an unknown factor which may vary considerably among the individual children studied. There are no means by which it can be regulated or measured with any degree of accuracy. With the exception of instances of familial exposure, one cannot even be certain that any exposure at all has occurred. Consequently, data relative to extrafamilial exposure may be unreliable and misleading. This is particularly true if the incidence of whooping cough in the general population is low. Under such conditions it is extremely difficult to ascertain whether apparently favorable results are due to the effectiveness of the vaccine or to the lack of exposure, unless an adequate number of vaccinated children are studied under satisfactory control conditions. The number of vaccinated children required for such an investigation will depend entirely on the number who are intimately exposed to whooping cough. When one is certain that there has been much exposure, as may occur during an outbreak in an institution, reliable results may be obtained with relatively few children. But when there is evidence of little exposure, as indicated by a low incidence of whooping cough, or when one is uncertain of the degree of exposure, as in instances of extrafamilial exposure, reliable results can be obtained only with a large group of children.

An admirable, almost perfect experiment with a large group of children in the general population was reported by Doull, Shibley and McClelland.[10] They found little difference between the incidence of whooping cough among the control children and the incidence among those vaccinated with 80 billion bacilli of a once-washed vaccine prepared from recently isolated strains. An experiment with a small group of children intimately exposed to whooping cough in an institution was recently reported by Goldberger,[1d] and me; we found that almost as many children had symptoms among those vaccinated with 80 billion bacilli of Sauer's vaccine as among the controls.

In both of these controlled experiments, one carried out in the general population of Cleveland and the other in a hospital for tuberculous patients in New York, the results indicated that doses of 80 billion bacilli of vaccines prepared from recently isolated strains did not prevent the development of whooping cough. In both experiments, however, the symptoms seemed to be milder, on the whole, among the

10. Doull, J. A.; Shibley, G. S., and McClelland, J. E.: Active Immunization Against Whooping Cough: Interim Report of Cleveland Experience, Am. J. Pub. Health **26**:1097, 1936.

vaccinated children than among the controls. This effect on the severity of the disease has been stressed by Madsen [3c] and by others.[11]

In the present study it seems apparent that the number of vaccinated children in each of the eight groups under consideration has proved to be inadequate for conclusive results, in view of the relatively few instances of known exposure and the low incidence of whooping cough during the period of observation. It is therefore difficult to be certain that the vaccinated children in each group were adequately exposed to the disease. Nor does one know whether the controls and the vaccinated children in each group were subjected to comparable conditions of exposure. Under such circumstances one cannot be certain that the differences between results obtained among vaccinated and among control children were due to chance or to the vaccine and its method of administration.

SUMMARY

In order to determine the prophylactic value of various whooping cough vaccines, 1,270 vaccinated children and 1,016 control children were followed up for fourteen to twenty-three months. There were eight groups of vaccinated children under consideration.

Familial exposure occurred in 1 per cent of all cases, and extrafamilial exposure was reported in 4.9 per cent.

There were 46 (3.6 per cent) cases of characteristic whooping cough among the vaccinated children, as compared with 43 (4.2 per cent) among the controls.

The incidence of characteristic whooping cough among the various groups of vaccinated children ranged from 0 to 6.72 per cent. It was lower among those inoculated with 80 billion bacilli than among those inoculated with smaller doses. One cannot be certain whether these differences were due to chance or to the vaccines, because of the relatively small number of children in each group, the low rate of exposure and the small number of cases of whooping cough in each of the various groups.

There were no occurrences of characteristic whooping cough in two groups, comprising a total of 294 children, who were inoculated subcutaneously with 80 billion bacilli of Sauer's vaccine or the vaccine of the New York Department of Health. Familial exposure occurred in only 1 case (0.3 per cent); no symptoms developed in this instance. Extrafamilial exposure was suspected in 10 (3.4 per cent) cases, in 3 of which there developed a cough unaccompanied by a whoop. In view of the low exposure rate, the factor of chance cannot be excluded in explaining the absence of characteristic whooping cough.

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11. Kendrick, P., and Eldering, G.: Progress Report on Pertussis Immunization, Am. J. Pub. Health **26**:8, 1936. Schorr, E. Y.: Prophylactic Pertussis Immunization, J. Pediat. **9**:49, 1936.

Doses of 50 billion bacilli or less seemed to have little, if any, prophylactic value; this also seemed to be true of doses of 80 billion bacilli of a vaccine prepared from a very old stock strain.

No beneficial effects were observed from the intradermal inoculation of part of the vaccine.

CONCLUSION

The determination of the prophylactic value of whooping cough vaccines has proved to be an extremely difficult problem, which has misled many investigators in the past. It is particularly likely to be misleading in experiments performed among children in the general population, because it is difficult to evaluate the degree of exposure to which the children have been subjected. For this reason, our own experience with over 2,000 children in New York has proved to be inadequate for conclusive results.

EFFECTS OF SERUM TRANSFER IN PATIENTS WITH RHEUMATIC FEVER

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The cause of rheumatic fever is still unknown. The disease attacks particularly children of the poorer economic classes, and it is therefore not surprising that it has been etiologically connected with three other disorders which prevail in the same group, viz., tuberculosis, streptococcic infections and vitamin deficiency diseases. No one has as yet succeeded, however, in demonstrating a direct link between these diseases and rheumatic fever.

The importance of the hemolytic streptococcus in producing rheumatic fever has been advanced by Coburn and Pauli,[1] who stated the belief that the reaction of the patient to certain well defined strains of hemolytic streptococci is the underlying cause of rheumatic fever. However, the reports of Wheeler and her associates,[2] whose material must have been drawn from the same vicinity as the material of Coburn and Pauli, contradicted this view. Until the results of investigators are in accord, the entire question must be considered unsettled.

Many observers have thought that various strains of nonhemolytic streptococci are responsible for rheumatic fever, and several reports have appeared concerning the isolation of various strains of these organisms from the blood of patients with rheumatic fever.[3] However, no one has been able to reproduce true rheumatic lesions in experimental

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1. Coburn, A. F., and Pauli, R. H.: J. Exper. Med. **62**:129, 137 and 159, 1935; J. Clin. Investigation **14**:755, 763 and 769, 1935.

2. Wheeler, G. W.; Wilson, M. G., and Leash, M. M.: J. Clin. Investigation **14**:345, 1935. Wilson, M. G.; Wheeler, G. W., and Leash, M. M.: ibid. **14**: 333, 1935.

3. Clawson, B. J.: J. Infect. Dis. **36**:444, 1925. Clawson, B. J.; Wetherby, M.; Hilbert, E. H., and Hilleboe, H. E.: Am. J. M. Sc. **184**:758, 1932. Birkhaug, K. E.: Proc. Soc. Exper. Biol. & Med. **24**:541, 1927.

animals with streptococci. Lichtman [4] found that the nonhemolytic streptococcus could be isolated from 6 per cent of a series of patients suffering from nine totally different diseases. It is established that the nonhemolytic streptococcus can be constantly obtained from almost every throat. In view of these facts, it would seem that the isolation of various strains of nonhemolytic streptococci from the blood stream of rheumatic patients is merely coincidental, serving as evidence that the most frequent transitory bacterium in the blood of all persons is a nonhemolytic streptococcus.

Many observers [5] have stated that all types of streptococci are able to produce an allergic reaction in certain persons and that perhaps organisms other than the streptococcus are able to do likewise. According to this school of thought, rheumatic fever is an expression of this allergic reaction. It is obvious that at the present time this theory can be neither proved nor disproved.

By the use of a special technic, several workers abroad [6] have isolated a tuberculosis organism in cases of acute rheumatic fever, but this work has not been confirmed. The reader is referred to the review of Tan [7] for further details.

Rinehart [8] was led to believe that rheumatic fever might be the result of vitamin C deficiency plus infection, but other workers [9] could find no clinical evidence for this hypothesis.[10]

Several English workers [11] have observed particles which strongly suggest virus elementary bodies in the exudates obtained from synovial and pericardial cavities of patients with rheumatic fever. To date, however, the evidence is indirect, and the disease has not been transmitted to experimental animals with this material.

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4. Lichtman, S. S., and Gross, L.: Streptococci in the Blood in Rheumatic Fever, Rheumatoid Arthritis and Other Diseases Based on a Study of 5,233 Consecutive Blood Cultures, Arch. Int. Med. **49**:1078 (June) 1932.

5. Swift, H. F.: Rheumatic Fever: Hektoen Lecture, Billings Foundation, J. A. M. A. **92**:2071 (June 22) 1929. Ritchie, W. T.: Tr. Med.-Chir. Soc. Edinburgh, 1934-1935, p. 117; in Edinburgh M. J., July 1935. Brown, G. I.: J. Lab. & Clin. Med. **20**:247, 1934. Traut, E. F.: M. Clin. North America **18**: 1237, 1935.

6. Reitter, C., and Löwenstein, E.: Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. 44, 1932, p. 224. Reitter, C.: Zentralbl. f. inn. Med. **56**:449, 1935.

7. Tan, Y. D.: Chinese M. J. **44**:139, 1935.

8. Rinehart, J. F.: Ann. Int. Med. **9**:586, 1935.

9. Schultz, M. P.: J. Clin. Investigation **15**:385, 1936. Faulkner, J. M.: New England J. Med. **213**:19, 1935.

10. Klein and his associates (in an unpublished study) found no evidence of decreased ascorbic acid in the blood of 26 patients with acute rheumatic fever.

11. Schlesinger, B.; Signy, A. G.; Amies, C. R., and Barnard, J. E.: Lancet **1**:1145, 1935. Coles, A. C.: ibid. **2**:125, 1935. Clarks, J. I., and Douglas, M.: Brit. M. J. **2**:247, 1931.

In short, one is forced to admit that the important known facts concerning rheumatic fever are as follows: 1. It is a disease frequently preceded by an infection of the respiratory tract. 2. It is a disease peculiar in regard to time (spring and fall), place (temperate zones) and persons (the young, poor children). 3. It attacks the mesenchymal tissues of the body. 4. It is characterized by a tendency to remission and exacerbation.

In view of the confusion surrounding the etiology of rheumatic fever, it appeared important to us to determine whether the blood of the patient with acute rheumatic fever when rendered bacteriologically sterile had any power to reproduce the disease in the same and in other patients when they were ostensibly convalescing from their acute attack. Similarly, it seemed important to determine if the blood of the patient convalescing from rheumatic fever or of the patient in whom the disease had been arrested was able to influence the course of the patient acutely ill with the disease.

METHODS

Both patients with acute rheumatic fever and those convalescing from the disease were bled under strict asepsis, approximately 175 to 200 cc. of blood being obtained and allowed to stand in the ice box for forty-eight hours. At the end of this time the serum was pipetted off and passed through the Berkefeld filter, and sufficient merthiolate was added to produce a concentration of 1:20,000 in the serum. The serum was then placed in rubber-stoppered sterile vaccine bottles and stored on ice until used. Before injection, the serum was subcultured twice, on blood agar and on dextrose beef broth, to ensure sterility, and it was always warmed to body temperature before injection. In making cross injections, it was ascertained that the donor did not suffer from syphilis and that his serum was compatible with the recipient's blood.

PROCEDURE WITH ACUTE RHEUMATIC FEVER SERUM

Blood was taken from 11 patients suffering from acute rheumatic fever and was treated as just described. The blood was secured on the first or second day after admission, and only 1 of the patients had received salicylate therapy when the blood was drawn. The patients so bled were given transfusions if it appeared necessary. All of these patients at the time that the blood was withdrawn had an elevation of temperature and pulse rate, a rapid sedimentation rate, endocardial involvement and present or recent articular involvement. The hemolytic streptococcus was demonstrated in the nasopalatine or pharyngeal flora in 9 of these cases, and it was the predominant organism in 5. Blood cultures were uniformly sterile. The sedimentation and the Weltmann test[12] were frequently performed on these patients throughout their course. When the temperature had been normal for a few weeks and the sedimentation and the Weltmann reaction had returned to a normal or a stable low level, serums taken from 7 of these patients were

12. Levinson, S. A.; Klein, R. I., and Rosenblum, P.: J. Lab. & Clin. Med. **23**:53, 1937.

injected intravenously, each into the patient from whom it was originally obtained. Each serum of the remaining 4 patients was injected intravenously into a patient other than the one from whom it was originally obtained. Thus each of 7 convalescent rheumatic patients received his own serum, which had been withdrawn from him during his acute illness, and each of 4 convalescent rheumatic patients received serum taken from another patient during the acute phase of rheumatic fever.

RESULTS WITH "ACUTE RHEUMATIC FEVER SERUM"

An inspection of table 1 shows that in 6 of the 7 patients receiving their own serum, obtained during the acute phase of their rheumatic

TABLE 1.—*Effect of Intravenous Injection of Acute Rheumatic Fever Serum During Convalescence*

Patient	Amount of Serum Cc.	Time Between Withdrawal and Injection of Serum, Days	Temperature Range During Week or Two Before Injection, F.	Maximum Temperature After Injection, F.	Average Pulse Rate During Week or Two Before Injection, Beats per Min.	Maximum Pulse After Injection, Beats per Min.	Duration of Reaction, Days	Joint Involvement	Time Lag After Injection Before Reaction, Days	Sedimentation Rate Just Before Injection, Mm. per Hour	Maximum Sedimentation Rate After Injection, Mm. per Hr.	Weltmann Reaction Just Before Injection	Weltmann Reaction After Injection
A. Patient's Own Serum													
J. W.	40	61	98- 99.0	101.0	110	120	2	None	11	3	15	9	7
R. Y.*	100	33	98- 99.0	100.2	85	100	2	Pain	11	19	..	..	..
D. J.	80	43	98- 99.4	101.0	185	140	1	None	9	9	24	6	5
K. E.*	120	57	99-100.0	101.0	105	120	5	Pain, swelling	3	24	31	6	4
G. T.†	60	70	98-100.0	100.8	100	120	2	None	8	43	25	6	9
W. O.	80	86	98- 99.8	100.4	100	100	1	None	5	23	..	7	..
L. A.*‡	97	49	98-100.0	100.0	90	90	0	None	0	42	25	4	5
B. Another Patient's Serum*													
J. G.	100	210	99-100.0	101.0	90	100	1	None	1	46	30	6	9
E. L.	110	180	99-100.0	100.0	95	85	0	None	0	20	15	6	6
R. L.	102	60	98-100.0	99.0	85	80	0	None	0	48	42	5	6
E. H.	57	211	98-100.0	100.0	90	85	0	None	0	56	33	5	6

* These patients had articular involvement when serum was withdrawn.
† This patient received a second injection of her own convalescent serum (withdrawn just prior to the injection of the acute serum) fourteen days after the injection of the acute serum. There was no reaction to the convalescent serum.
‡ This patient had received large quantities of salicylates on the day the acute serum had been withdrawn.

fever, there were indications that this serum provoked some type of reaction, an increase in pulse rate and an elevation in temperature being the most common manifestations. It is to be noted that 2 of these patients experienced evidence of articular involvement and that 3 of them had changes in the sedimentation rate and in the Weltmann reaction which were concomitant with the elevation of temperature and pulse rate. It is possible that the peak of change might have been missed, since these two tests were done weekly or semiweekly. It is also interesting to observe that in these 6 cases there was a lag of days before the reactions which followed injection appeared.

In contrast to the results obtained after the injection of acute rheumatic fever serum into the patient from whom it was originally obtained, the 4 patients receiving such serum from other patients showed no reaction, with 1 exception. In this exception the reaction occurred immediately, and hence we are inclined to view this as a nonspecific serum reaction. Perhaps the difference between these two groups may be attributed either to greater age of the serum or to its administration earlier during convalescence in the group receiving serum from other patients, although it is possible that specificity may be the explanation.

A case in which a reaction followed intravenous injection of acute rheumatic fever serum into the patient from whom it was originally obtained is reported here in detail:

REPORT OF A CASE

K. E., a 13 year old girl, entered the Cook County Hospital in the service of one of us (P. R.) on Feb. 18, 1937, with redness, pain, tenderness and swelling of the left wrist and the left middle finger, as well as pain and tenderness of both shoulders. She had a temperature of 103.6 F. and a pulse rate of 100.

The patient's present illness began when she caught a cold from her father on January 15, which cleared up on February 1. On February 5 the patient began to notice pain in the sole of her right foot, which began to swell and redden on the following day. Then she had migrating polyarthritis, which involved both ankles, shoulders and wrists. She had noticed fever throughout this involvement.

The patient had contracted scarlet fever seven years previously, and while in the hospital recovering from this infection she had migrating polyarthritis, which lasted a month. Since this bout of scarlet fever the patient had had frequent pain in the muscles and stiffness of the joints.

There was no history of soreness of the throat, epistaxis, vomiting or cardiac symptoms. The remainder of the history was noncontributory.

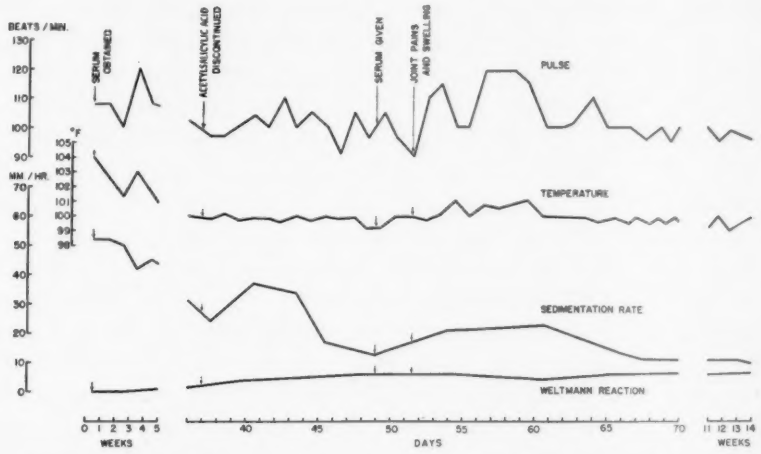
The patient had a temperature of 103.6 F. on admission to the hospital, but the pulse rate was only 100. There was a slight systolic murmur at the cardiac apex and in the aortic area, but the heart was not enlarged. There were well defined redness, tenderness and swelling of the left wrist and the left middle finger, as well as tenderness of both shoulders. The pharynx and tonsils were injected. The hemoglobin content on admission was 60 per cent (Sahli); the red cell count was 4,000,000 and the white cell count 9,050. The electrocardiogram revealed no abnormalities. A culture of material from the throat revealed no hemolytic streptococci (also absent from 3 subsequent cultures).

Approximately 210 cc. of blood was drawn from the patient on February 18 (the day of admission). She was not given salicylates until the sixth day of hospitalization, and until that time the temperature continued to vary between 100 and 104 F., with constant articular involvement. After the administration of salicylates the patient's temperature fell, but the articular symptoms continued intermittently, though with lessened intensity, until April 3, when they disappeared completely. Salicylates were then discontinued.

On April 15 approximately 120 cc. of the patient's own serum was injected intravenously. There was no reaction of any sort until April 18, when the

middle finger of the left hand began to swell and redden and the girl was unable to flex it. This involvement disappeared on April 19, although on this same day the temperature rose slightly above 100 F. From April 21 to 26 the patient had an elevation of temperature, which daily reached a peak of 101 F. There was no articular involvement during this period, and other than the elevation of pulse rate and temperature there were no physical signs or symptoms of exacerbation of the disease. After this bout of fever and elevation of pulse rate the patient had no abnormal developments. On May 11 she had her tonsils removed, without any subsequent rheumatic flare-up.

The chart summarizes the essential findings before and after the injection of serum.



Summary of findings for K. E. before and after the injection of serum.

TABLE 2.—*Effect of Intravenous Injection of Convalescent Rheumatic Fever Serum During Acute Rheumatic Fever*

Patient	Amount of Convalescent Serum, Cc.	Was There Further Articular Involvement?	Did Temperature Decrease in Next 5 Days?	Did Pulse Rate Decrease in Next 5 Days?	Did Sedimentation Rate of Weltmann Reaction Show Signs of Improvement Next 10 Days?	Duration of Acute Symptoms Following Injection
K. B.	140	Yes	No	No	No	92 days
W. O.	110	Yes	No	No	No	102 days
L. A.	92	Yes	Yes	Yes	No	65 days
B. R.	30	Yes	No	No	No	50 days

PROCEDURE WITH CONVALESCENT RHEUMATIC FEVER SERUM

Blood was taken from 4 patients who had just recovered from an attack of acute rheumatic fever and was treated exactly as described for acute rheumatic fever serum. These convalescent rheumatic fever serums were injected intravenously into 4 patients suffering from severe attacks of acute rheumatic fever, as evidenced by acute articular involvement, cardiac involvement, high temperature, increased sedimentation rate and a Weltmann reaction far to the left.

RESULTS WITH CONVALESCENT RHEUMATIC FEVER SERUM

From table 2, in which the results are summarized, it becomes apparent that no noticeable improvement could be detected in the condition of any of these patients except possibly in 1 instance (L. A.). The course of the disease was apparently not abbreviated when compared to the course of the 11 patients who did not receive this type of therapy.

COMMENT

In a disease as variable as rheumatic fever, it is difficult properly to evaluate observations such as ours. The small changes in temperature, pulse rate and sedimentation rate in some of the patients who received their own "acute" serum may have been due to factors other than a specific substance contained in the injected serum. It is regrettable too that the small quantity of serum used, the age of the serum and its Berkefeld filtration all doubtlessly tended to minimize the reaction which could be obtained. For these reasons, it is not surprising that the findings are not as clearcut as we should have liked. However, they are suggestive. If confirmed, our results indicate the probability that there is some substance in the blood of the patients with acute rheumatic fever which is able to reproduce symptoms and signs strongly suggestive of the disease when the serum of this blood is injected intravenously into the patient from whom it was originally taken. The long lag of three to eleven days after injection before any reaction was observed confirms this impression. Spontaneous exacerbations would appear to be ruled out because the reactions were of such short duration, in no case lasting longer than five days. The failure to produce the reaction in the instances when acute serum from another patient was injected tends to show that the reaction obtained with the patient's own acute serum was not a nonspecific serum reaction.

Our results do not support the view advanced by Archer [13] and his associates that convalescent rheumatic fever serum may be of value in acute rheumatic fever. They reported that the intramuscular injection of 5 to 13 cc. of convalescent serum into 4 patients gave sufficiently suggestive results to warrant further clinical trial. We injected 30 to 140 cc. of convalescent serum intravenously into 4 patients without detecting any later evidence of clinical improvement.

CONCLUSIONS

Serum originally obtained from patients during the acute phase of rheumatic fever was injected intravenously into the same patients during convalescence. After a lag of days, this evoked symptoms and signs suggestive of the original disease in 6 of 7 patients.

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13. Archer, B. H.; Garfield, W., and Zarno, C.: Arch. Pediat. **53**:87, 1936.

The same type of serum was obtained from patients during the acute phase of rheumatic fever and was injected intravenously into other patients during convalescence. This produced a slight immediate reaction during the first twenty-four hours in 1 patient and no reaction at all in the other 3 tested.

No evidence of any beneficial effect followed the use of convalescent serum in 4 patients with acute rheumatic fever.

Dr. L. N. Katz gave advice and criticism and Dr. K. Howell gave suggestions in this study.

Case Reports

PERITONITIS DUE TO THE MORGAN BACILLUS

WITH A BRIEF REVIEW OF LITERATURE ON THE PATHOGENICITY OF THIS ORGANISM

ERWIN NETER, M.D.
AND
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In 1906 and 1907, Morgan [1] published a comprehensive study of the bacteriology of summer diarrhea in infants. He described for the first time a micro-organism which he considered to be of etiologic significance in this disease and which today bears his name. In 1909 Morgan and Ledingham [2] described four more types of organism, which are referred to in the literature as Morgan bacilli types V, X, XII and XIV. Numerous investigators, including Ohrum and Bahr,[3] Phalen and Kilburne,[4] Lewis,[5] Alexander,[6] Bahr and Ohrum,[7] Archibald, Had-

From the Laboratory of the Children's Hospital and the Laboratory of the Department of Pathology and Bacteriology of the University of Buffalo School of Medicine.

1. Morgan, H. de R.: Upon the Bacteriology of the Summer Diarrhea of Infants, Brit. M. J. **1**:908-912, 1906; **2**:16-19, 1907.

2. Morgan, H. de R., and Ledingham, J. C. G.: The Bacteriology of Summer Diarrhea, Proc. Roy. Soc. Med. (Epidem. Sect.) **2**:133-158, 1909.

3. Ohrum, T., and Bahr, O. F.: Meddelelser fra vet. Kgl. veterinaer og landbohoiskoles serumlaboratorium, 1910, no. 5, p. 210.

4. Phalen, J. M., and Kilburne, E. D.: The Bacteriology of an Epidemic of Bacillary Dysentery, Mil. Surgeon **26**:433-443, 1910.

5. Lewis, C. J.: Report on the Results of an Examination of the Feces of Children with Special Reference to the Occurrence of Bacilli Which Neither Liquefy Gelatine Nor Ferment Lactose, in supplement to Fortieth Annual Report of the Medical Officer of the Local Governing Board of London, 1910-1911, no. 2, appendix B, p. 314; Report on the Prevalence and Character of Non-Lactose Fermenting and Non-Liquefying Aerobic Bacilli in the Feces of Young Children Under Normal Conditions and in Epidemic Diarrhea During 1911, in Forty-First Annual Report of the Medical Officer of the Local Governing Board of London, 1911-1912, no. 2, appendix B.

6. Alexander, D. M.: Report on the Prevalence and Character of Non-Lactose Fermenting and Non-Liquefying Aerobic Bacilli in the Feces of Young Children Under Normal Conditions and in Epidemic Diarrhea During 1911, in Forty-First Annual Report of the Medical Officer of the Local Governing Board of London, 1911-1912, no. 3, appendix B, p. 288; Report on the Prevalence and Character of

(Footnotes continued on next page)

field, Logan and Campbell,[8] d'Hérelle,[9] Logan,[10] Tribondeau and Fichet,[11] Jungmann and Neisser,[12] Seligman,[13] Rey,[14] Besson and de Lavergne,[15] Dopter,[16] Dick, Dick and Williams[17] and D'Aunoy,[18] described the occurrence of Morgan bacilli in the stools of children with summer diarrhea and also in patients (both children and adults) with enteritis and with typical or atypical dysentery.

The etiologic significance of the Morgan bacillus, however, has not found general agreement. Some authors, including Davison,[19] Thjötta[20] and Gardner,[21] have expressed the belief that the Morgan bacillus is not the causative agent of these diseases but rather a nonpathogenic

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Bacilli Occurring in the Feces of Young Children Under Normal Conditions and in Epidemic Diarrhea, in Forty-Second Annual Report of the Medical Officer of the Local Governing Board of London, 1912-1913, no. 4, appendix B, p. 384.

7. Bahr, O. F., and Ohrum, T.: Meddelelser fra vet. Kgl. veterinaer og landbohoiskoles serumlaboratorium, 1912, no. 19, p. 66.

8. Archibald, R. G.; Hadfield, G.; Logan, W., and Campbell, W.: Reports of the M. & H. Laboratories Dealing with the Diseases Affecting the Troops in the Dardanelles, J. Roy. Army M. Corps, London **26**:695-724, 1916.

9. d'Hérelle, F.: Contribution á l'étude de la dysentérie: Nouveaux bacilles dysentériques, pathogènes pour les animaux d'expérience, Bull. Acad. de méd., Paris **76**:425-428, 1916.

10. Logan, W. R.: The Bacteriology of the Feces in Diarrhea of Infants, Lancet **2**:824-827, 1916.

11. Tribondeau, L., and Fichet, M.: Note sur les dysentéries des Dardanelles, Ann. Inst. Pasteur **30**:357-362, 1916.

12. Jungmann, P., and Neisser, E.: Zur Klinik und Epidemiologie der Ruhr, Med. Klin. **13**:122-127, 1917.

13. Seligman, E.: Zur Bakteriologie der Ruhr im Kriege, Zentralbl. f. Bakt. (Abt. 1) **79**:71-79, 1917.

14. Rey, J. F.: A Fatal Case of Dysentery in an Adult Caused by Morgan's Bacillus, Practitioner **104**:466-467, 1920.

15. Besson, A., and de Lavergne: Les infections à bacille de Morgan chez l'adulte, Paris méd. **11**:449-453, 1921.

16. Dopter, J. M.: Le pourvoir pathogène des Bacilles de Morgan et de Castellani, Bull. Acad. de méd., Paris **85**:301, 1921.

17. Dick, G. F.; Dick, G. H., and Williams, J. L.: The Etiology of an Epidemic of Enteritis Associated with Mastoiditis in Infants, Am. J. Dis. Child. **35**: 955-963 (June) 1928.

18. D'Aunoy, R.: Infections Probably Due to Morgan's Bacillus, Am. J. M. Sc. **178**:834-837, 1929.

19. Davison, W. C.: Bacillary Dysentery in Children, Bull. Johns Hopkins Hosp. **31**:225-234, 1920; A Bacteriological and Clinical Consideration of Bacillary Dysentery in Adults and Children, Medicine **1**:389-510, 1922.

20. Thjötta, T.: (*a*) On the Bacillus of Morgan: No. 1—Meta-Colon-Bacillus, J. Bact. **5**:67-77, 1920; (*b*) Septic Infection Due to Bacterium Morgani I, J. Infect. Dis. **43**:349-352, 1928.

21. Gardner, H. D., in Bensted, H. J., and others: A System of Bacteriology in Relation to Medicine, Medical Research Council, London, His Majesty's Stationery Office, 1929, vol. 4, pp. 179-184.

micro-organism which happens to be found more frequently in patients with intestinal disturbances. These authors stress as the chief reasons for their denial (1) the absence of production of antibodies by the patients in whom the bacillus is found and (2) the occurrence of Morgan bacilli in healthy persons and in patients suffering from other than intestinal diseases. Ten Broeck and Norbury [21a] assumed an intermediate position; they said that the Morgan bacillus may influence the factors which cause the diarrhea, but that the diarrhea itself is started by other organisms—for instance, by the dysentery bacillus. During the past year, in our laboratories, the Morgan bacillus type I has been isolated from the feces of 5 children with diarrhea; dysentery bacilli or other pathogenic organisms were not recovered in these cases. In none of the patients did specific antibodies develop. It could be shown that we were not dealing with a small epidemic, since, aside from other reasons, the strains of Morgan bacilli belonged to different serologic types. As may be seen from this brief review, the pathogenic significance of the Morgan bacillus in summer diarrhea of children and in other intestinal diseases is still a moot question.

There can be no doubt, however, that the Morgan bacillus may be the cause of diseases other than intestinal. Morgan bacilli were found in cases of septicemia reported by D'Aunoy,[18] Thjötta,[20b] Magath and Jackson [22] and Gittins and Hawksley.[23] In 1929, Havens and Ridgway [24] described a small epidemic of 13 cases of paratyphoid-like fever which was due to the Morgan bacillus. In a later communication, Havens and Mayfield [25] reported 49 cases of paratyphoid-like fever. In 6 of these, Morgan bacilli were isolated from the blood stream; in 11, the bacilli were present in the urine, and in 43, the patients had a significant high titer of specific agglutinins in their serums. Thjötta [20b] reported a case of infection of the gallbladder due to the Morgan bacillus. Several authors, among them D'Aunoy,[18] Riding [26] and Waaler,[27] described cases

21a. Ten Broeck, C., and Norbury, F. G.: The Presence of B. Dysenteria, B. Proteus Vulgaris, Bact. Welchii and Morgan's Bacillus No. 1 in the Stools of Cases of Infectious Diarrhea, Boston M. & S. J. **173**:280-284, 1915.

22. Magath, T. B., and Jackson, E.: Septicemia Due to the Bacillus of Morgan No. 1, M. Clin. North America **8**:1381-1387, 1925.

23. Gittins, R. J., and Hawksley, J. C.: Meningitis and Septicemia Due to Morgan's No. 1 Bacillus, Lancet **1**:1040-1042, 1932.

24. Havens, L. C., and Ridgway, C.: The Pathogenicity of Morgan's Bacillus: A Series of Thirteen Cases Attributable to Infection with This Organism, J. Prev. Med. **3**:159-165, 1929.

25. Havens, L. C., and Mayfield, C. R.: A Paratyphoid-Like Infection Due to Morgan's Bacillus, J. Prev. Med. **4**:179-188, 1930.

26. Riding, D.: Pyelitis from Infection with Morgan's No. 1 Bacillus, Brit. M. J. **1**:183-184, 1927.

27. Waaler, E.: Five Cases of Infection of the Urinary Tract, J. Bact. **22**:261-273, 1931.

of infections of the urinary system which were caused by this Morgan bacillus. In the 5 cases reported by Waaler, the micro-organisms were Morgan bacilli of type XII. A case of mastoiditis with sinus thrombosis was observed by King.[28] Mastoiditis occurring as complication in an epidemic of enteritis was described by Dick, Dick and Williams [17] and by Sutton.[29] Of special interest are cases of meningitis due to the Morgan bacillus, as described by Gittins and Hawksley,[23] Mitchell [30] and Bier and Lange.[31] Finally, it may be mentioned that the Morgan bacillus can cause various diseases in animals.

We shall report here a case of purulent peritonitis due to the Morgan bacillus type XIV.

REPORT OF A CASE

A boy 11 years of age became acutely ill, with vomiting and with pain around the umbilicus, the day prior to admission to the hospital. On his admission, the temperature was 100.6 F., the pulse rate 112 and the respiratory rate 24. On physical examination, tenderness was found above both lower quadrants of the abdomen; no mass was palpable. The white blood cell count showed 21,000 leukocytes with 80 per cent polymorphonuclear cells. The urine showed a specific gravity of 1.035, an acid reaction and the presence of a trace of albumin; the result of the microscopic examination of the urinary sediment was essentially negative. A diagnosis of appendicitis was made and operation was performed. When the peritoneum was opened, a great deal of purulent material was found and was aspirated with a suction machine. The entire appendix was acutely inflamed; there was a small perforation in its distal portion. After the appendectomy, a drain was inserted. The patient made an uneventful recovery.

The bacteriologic examination of the peritoneal exudate showed a pure culture of a gram-negative bacillus which had the characteristic properties of Morgan bacillus type XIV.[32] It fermented: dextrose, maltose, mannitol, galactose and levulose, with the production of acid and gas; it failed to ferment, within two weeks' incubation at 37 C., lactose, sucrose and dulcitol. It produced indole within twenty-four hours. Litmus milk was rendered acid after twenty-four to forty-eight hours and became slightly alkaline after ten days' incubation. Gelatin was not liquefied. Agglutination tests with this micro-organism gave negative results with the following anti-serums: typhoid serum, paratyphoid A and paratyphoid B

28. King, E. D.: Mastoiditis with Sinus Thrombosis Due to Bacillus Morgani, J. Med. **18**:303-304, 1937.

29. Sutton, T. L.: Pseudomembranous Enterocolitis and Mastoiditis Associated with Infection with Morgan's Bacillus, Am. J. Dis. Child. **31**:814-817 (April) 1929.

30. Mitchell, R. H.: Meningitis Due to the Morgan Bacillus, J. Pediat. **9**: 791-794, 1936.

31. Bier, O. G., and Lange, O.: Ueber das Vorkommen des Bacillus Morgan No. 1 im Liquor bei einem Meningitisfall, Zentralbl. f. Bakt. (Abt. 1) **138**:483-485, 1937.

32. The cultural characteristics and the antigenic structure of Morgan bacillus were thoroughly studied by E. O. Jordan, R. R. Crawford and T. McBroom (The Morgan Bacillus, J. Bact. **29**:131-148, 1935) and by K. F. Rauss (The Systematic Position of Morgan's Bacillus, J. Path. & Bact. **42**:183-192, 1936), who also reviewed the literature on the subject.

serums, Bacillus enteritidis serum, Bacillus aertrycke serum and polyvalent Bacillus coli antiserum. On intravenous injection of this micro-organsim into rabbits, specific agglutinins were produced. As for its pathogenicity in animals, this strain caused death of mice within twenty-four hours after intraperitoneal injection; culture of the heart's blood showed a pure growth of the Morgan bacillus. Similar results were obtained with guinea pigs. In rabbits, severe diarrhea developed after intravenous injection of a heat-killed or of a formaldehydized suspension.

Examination of the feces of the patient obtained the day after the operation revealed the presence of Bacillus coli communior, Bacillus coli communis and Streptococcus faecalis. Morgan bacilli were not found in the feces on several occasions. The serum of the patient was examined for agglutinins against the strain of the Morgan bacillus type XIV which had been recovered from the peritoneal exudate. Specimens of serum were obtained three days, eight days and three weeks after the onset of the disease, but at no time was agglutination with the patient's strain observed, not even with serum diluted 1 to 10. This is in accord with the observation of Gittins and Hawksley,[23] who reported a case of septicemia due to the Morgan bacillus in which agglutinins failed to develop. These observations stress the point that absence of specific agglutinins against bacteria does not necessarily exclude their pathogenic significance.

SUMMARY

A case of diffuse purulent peritonitis due to the Morgan bacillus type XIV and following appendicitis is reported. The patient, who made an uneventful recovery after operation, failed to acquire specific agglutinins.

A brief review of the literature shows that the pathogenic significance of the Morgan bacillus in summer diarrhea of children and in other intestinal infections is not yet definitely established. On the other hand, the bacillus can be pathogenic for man and may cause diseases such as septicemia, infections of the biliary and urinary system, mastoiditis, meningitis and—as in the case reported here—peritonitis.

GANGRENE OF THE TOES FOLLOWING PNEUMOCOCCEMIA

TREATMENT WITH SULFANILAMIDE

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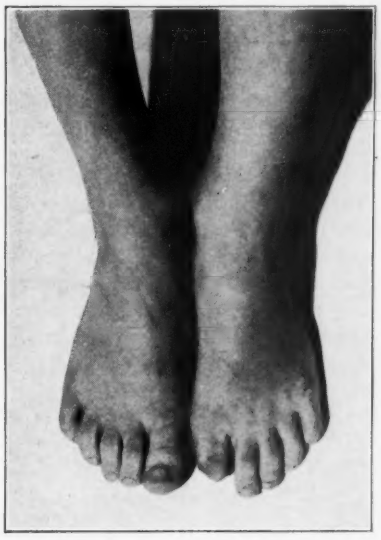
The following case, in which the condition was diagnosed as septic thrombi with gangrene of the toes following pneumococcemia, is reported as an illustration of successful treatment with sulfanilamide.



End result of the gangrenous process in the left big toe.

REPORT OF A CASE

On July 6, 1937, I was asked by Dr. Pansy, of South River, N. J., to see with him in consultation Henry M., aged 9 years.

The history of the case was as follows: The illness had begun with fever on June 28, and two days later cough, pain in the left side of the chest posteriorly and blood-tinged expectoration followed. On July 2 the patient complained of pain in the region of the toes of both feet, and the next day both big toes became reddened and painful. After another day or two, they had become blackish.

Examination showed the boy to be well developed but markedly undernourished. He was acutely ill, with face flushed, alae nasi dilated and lips cyanotic. There were coughing and dyspnea. The throat was red. Auscultation revealed dulness, bronchial breathing and moist rales at the base of the left lung. There was

gangrene of the big toes, with a seropurulent exudate, the process in the left big toe being the more extensive. The pulsations of the dorsalis pedis artery appeared normal on both sides. Results of the physical examination otherwise were negative.

I immediately referred the boy to my service at St. Peter's General Hospital, and he was admitted the same day. On admission the temperature was 102.4, the pulse rate 126 and the respiratory rate 40. Cultures of the blood and of the exudate from the left big toe were later reported as showing a pneumococcus of group IV. A second culture of the exudate, made later, revealed a pneumococcus of type VI.

The blood count on admission showed 3,640,000 red cells, with 57 per cent hemoglobin, and 13,400 white cells, with 63 per cent neutrophils, 35 per cent lymph and 2 per cent mononuclears. The urine had a specific gravity of 1.015, and showed the presence of albumin (2 plus), red blood cells (2 plus), occasional white blood cells and occasional hyaline casts. The next specimen, examined two days later, was normal. The blood sugar on admission was 107 mg. per hundred cubic centimeters.

Treatment consisted of administration of 30 grains (1.94 Gm.) of sulfanilamide daily, increased after the first two days to 40 grains (2.59 Gm.), an occasional dose of phenobarbital to control the pain in the toes and the restlessness, and, for the lower extremities, warm, wet dressings of magnesium sulfate and the use of a cradle containing an electric light bulb.

The response to the treatment was almost immediate, the boy showing moderate improvement on the day after admission, July 8. On the third day after admission the temperature dropped suddenly to 100.3, and from then on it never rose again, becoming normal on the fourteenth day. As for the gangrene of the big toes, the flexor surface of the left one became more and more discolored and finally sloughed off, while the color of the extensor surface of both the left and the right big toe gradually turned normal (fig.).

The result of a second blood culture, made on July 15, eight days after the first, was reported negative on July 17, 19 and 21.

The boy was discharged from the hospital in good condition on August 14.

127 Livingston Avenue.

Case Reports

ERYTHROPHAGOCYTOSIS IN ANEMIA OF THE NEWBORN

REPORT OF THREE CASES

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AND

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It is the purpose of this paper to describe briefly 3 cases of severe anemia of the newborn. In the circulating blood of 2 of the patients concerned, considerable evidence of phagocytosis of the erythrocytes was found. In the third, seen and treated earlier after birth than the other 2, there was some evidence of such phagocytosis.

ANEMIA OF THE NEWBORN

A full discussion of anemia of the newborn is not needed here. Since 1919, the time when Ecklin [1] first described in detail this type of anemia, various writers, among them Pasachoff and Wilson,[2] Abt,[3] Diamond, Blackfan and Baty,[4] Abbott and Abbott,[5] Dennett and Ashton [6] and Huenekens,[7] have reviewed the subject, collected the cases

Read before the Society for Pediatric Research at Atlantic City, May 4, 1937.

From the Department of Pediatrics and the Department of Clinical Pathology, Syracuse University College of Medicine.

1. Ecklin, T.: Ein Fall von Anämie bei einem Neugeborenen, Monatschr. f. Kinderh. **15**:425, 1919.

2. Pasachoff, H. D., and Wilson, L.: Congenital Anemia of the New-Born, Am. J. Dis. Child. **42**:111 (July) 1931; Am. J. Obst. & Gynec. **29**:415 (March) 1935.

3. Abt, A. F.: Anemia of the New-Born, Am. J. Dis. Child. **43**:337 (Feb.) 1932.

4. Diamond, L. K.; Blackfan, K. D., and Baty, J. M.: Erythroblastosis Fetalis and Its Association with Universal Edema of the Fetus, Icterus Gravis Neonatorum and Anemia of the Newborn, J. Pediat. **1**:269 (Sept.) 1932.

5. Abbott, K. H., and Abbott, F. F.: Idiopathic Anemia of the New-Born, Am. J. Dis. Child. **49**:724 (March) 1935.

6. Dennett, R. H., and Ashton, L. O.: Anemia of the Newborn, New York State J. Med. **34**:595 (July 1) 1934.

7. Huenekens, E. J.: Anemia of the New Born, J. Pediat. **9**:427 (Oct.) 1936.

in the literature and added their own cases. A full bibliography [8] on this subject shows that the number of reasonably definite cases, including those of this report, is well in the seventies.

It seems doubtful that the occurrence of this disease is as infrequent as the number of reports in the literature would suggest. Two factors which may account for the small number are: first, the varying degree of icterus which may clinically mask the anemia; second, the confusion which exists as to the classification and possible relationship of anemia of the newborn, icterus gravis and erythroblastosis.

ERYTHROPHAGOCYTOSIS IN INFANTS

In 1909, ten years before Ecklin's report was made, Buchan and Comrie [9] described the occurrence of phagocytosis of the erythrocytes in smears of blood taken at birth from the umbilical cords of two siblings who died of "congenital anemia with jaundice and enlargement of the spleen." It is interesting and perhaps significant that they fully described also the case of another baby in this family who probably had anemia of the newborn. Their report is the first which we have been able to locate of erythrophagocytosis in infancy. In 1912, Connal [10] described such a condition observed in the circulating blood of native South African children, 1 year of age and over, who were infested with malarial parasites. In 1932, Abt [3] described phagocytosis of erythrocytes in a case of anemia of the newborn, having previously [11] discussed in some detail its occurrence in other conditions and the possible histogenesis of the phagocytes involved in his case, which apparently were both monocytes and lymphocytes.

Diamond, Blackfan and Baty [4] alluded to erythrophagocytosis in W. J. Oatway's case of icterus gravis neonatorum, giving the reference as "unpublished data." We have not been able to find that Oatway's case has been reported subsequently. That case, however, together with Buchan and Comrie's 2 cases and Abt's case, makes a total of 4 cases of anemia or jaundice of the newborn in which erythrophagocytosis has been mentioned.

We wish to add 3 cases and to point out the striking similarity in every respect between our first case and the case described by Abt.

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8. Unpublished data.

9. Buchan, A. H., and Comrie, J. D.: Congenital Anemia: Four Cases with Jaundice and Enlargement of the Spleen, J. Path. & Bact. **13**:398, 1909.

10. Connal, A.: Auto-Erythrophagocytosis in Protozoal Diseases, J. Path. & Bact. **16**:502 (April) 1912.

11. Abt, A. F.: Mononuclear Erythrophagocytosis in the Blood of a New-Born Infant, Am. J. Dis. Child. **42**:1364 (Dec.) 1931.

REPORT OF CASES

CASE 1.—C. W.,[12] a girl, was born at full term with normal delivery on Dec. 18, 1935. The mother had ether anesthesia. The child's weight at birth was 7 pounds 9 ounces (3,430 Gm.); breathing was spontaneous, the color normal and the cry vigorous. The baby's color was not unusual until the fourth day, when icterus appeared. This continued for several days, but there was nothing sufficiently unusual about the child to be called to a physician's attention until the eleventh day, when, as the icterus had definitely begun to clear, it became apparent that the baby was quite pale. (It is true, however, that in a nurse's notes on the fifth day it was recorded that the baby was both jaundiced and pale.) The only important conditions observed in the complete physical examination on the eleventh day were the extreme pallor of skin and of mucous membranes, a systolic murmur heard over the entire precordium and the fact that the tip of the spleen was palpable about 1 cm. below the costal border.

The patient was the third sibling of a mother aged 24 and a father aged 37. The mother is English, and the father is of French Canadian descent. They are not related. The mother and her family, with the exception of her father, are people without much color; however, the only unusual feature of her complete blood count, made a month and a half after the baby's birth, was 12 per cent monocytes. Her diet during pregnancy was not remarkable. The father's personal and family histories show no evidence of anemia. He is of the dark plethoric type, in direct contrast to the mother. The Wassermann reactions of both parents were negative at the time the infant was born.

The patient's two brothers, born February 1933 and October 1934, respectively, are of normal size and weight, but the mother states that soon after birth the older child was extremely pale. He is still rather pale, but examination of the blood shows nothing remarkable.

A fourth infant, a girl, was born to the mother June 28, 1937. At the present writing this child has shown no abnormalities of any sort.

Progress.—The pallor continued to be marked, with perhaps a slight yellowish tinge, until the baby was about 3 weeks old. At this time, improvement, as shown by appearance and by examination of the blood, was definite. However, even during the period of icterus and of extreme pallor, she had continued to act normally with reference to eating, sleeping, gaining weight, movements and vigor of crying. Treatment in the hospital consisted of administration of 25 cc. of the father's blood intramuscularly on the eleventh day of life, 22 cc. on the sixteenth day, 20 cc. on the nineteenth day and 20 cc. on the twenty-fourth day. In addition, on the seventeenth day 30 cc. of citrated blood of the father was given intravenously. Iron and copper were given in small amounts by mouth, beginning on the fourteenth day. Roentgen examination of the long bones and skull failed to reveal any evidence of pathologic changes. The baby was discharged from the hospital on the twenty-ninth day of life and has been followed since that time in the outpatient clinic.

Examination of the Blood and Bone Marrow (fig. 1).—Although the main data on the blood are given chronologically in the table, certain observations are not included. Mitotic figures in erythroblasts were found rather frequently in the circulating blood during the period from the twelfth to the twentieth day of life, but have not been found since. Polychromasia and basophilic stippling were

12. This case is taken from the records of the pediatric service of the General Hospital of Syracuse. Dr. Robert Schwartz gave permission for us to study the case.

noted during the first week of the anemia. So-called basket cells and smudges of leukocytes were fairly numerous in the smears during the same period. Atypical mononuclear cells, apparently of the monocytic group, were present in small numbers through the whole course up until the last count (November 1936). Many of these cells had round, clear spaces the size of erythrocytes or smaller and

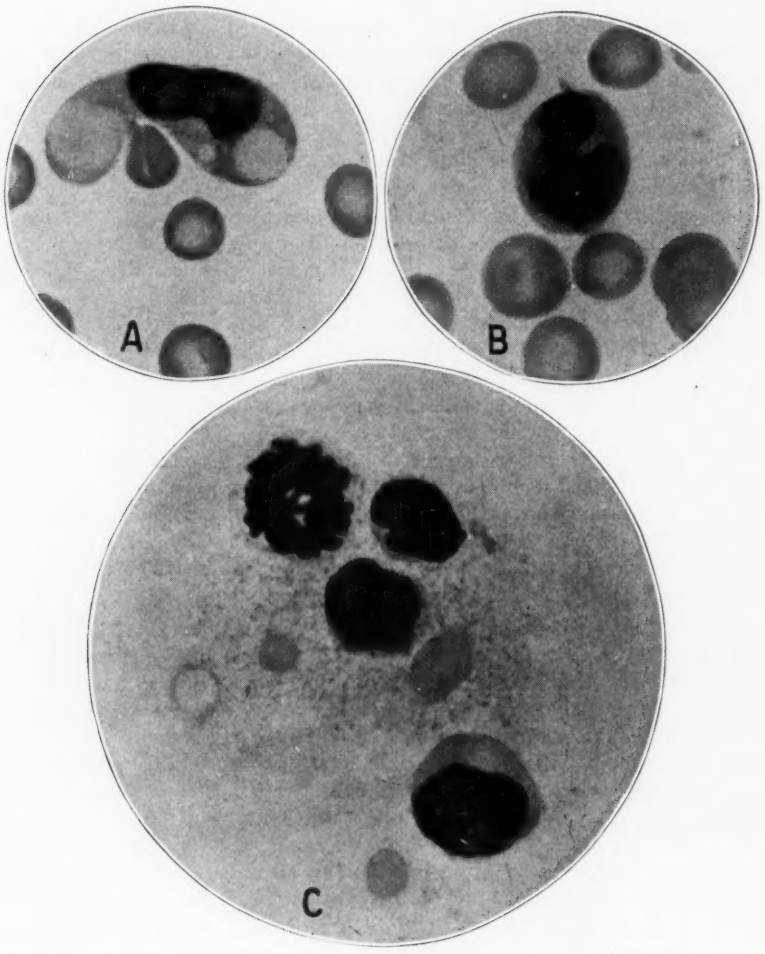

Fig. 1 (case 1).—*A*, blood smear (× 1,200, Wright stain) showing a phagocyte which contains, at the left, an erythrocyte with stained hemoglobin. In the same cell the circular spaces to the right appear unstained. *B*, blood smear (× 1,200, Wright stain) showing a phagocyte which contains a nucleus resembling that of an erythroblast. *C*, marrow smear (× 1,200, Wright stain) from a puncture of the sternum, showing a cell in mitotic division, two erythroblasts and a probable myeloblastic cell.

resembled the cells in which definitely stained erythrocytes were found. The platelet count on the twentieth day of life was 134,000 and four months later was 350,000. Coagulation and bleeding times were normal on the eleventh day, when the first counts were made. The icteric index was 40 on the sixteenth day of life. The result of the fragility test was normal on that day. During the period of most prominent anemia there seemed to be a definite macrocytic tendency, an observation which was confirmed by Dr. John Van Duyn, who determined by the use of a Leitz ocular micrometer the mean diameters in all 3 cases, as recorded in the chart.

A puncture of the head of the sternum with a large needle was made on the eighteenth day of life. Marrow tissue was obtained and studied in stained smears.

Blood Counts in Three Cases of Erythrophagocytosis in Anemia of the Newborn

		Hemoglobin	Erythrocytes					Leukocytes				
								Granulocytes, %				
	Age*	Content in Gm. per 100 Cc.	Total	Mean Diameter	Reticulocytes, %	Nucleated per 100 W.B.C.	Erythrophagocytes (Total Found)	Total	Immature	Mature	Lymphocytes, %	Monocytes, %
Case 1: C. W.	11	5.5	1.3	....	..	2	3	15.7	16	43	33	8
	12	4.8	1.4	8.01	16	13	10	36.0	16	42	35	7
	16	4.8	1.4	....	20	32	4	18.0	7	47	36	10
	17	...	...	8.24	..	41	3	14.8	7	45	43	5
	18	...	1.4	....	..	76	6	11.9	11	47	33	9
	20	5.3	1.6	....	21	25	2	12.8	6	33	52	9
	23	6.5	1.9	8.50	26	29	..	9.3	9	25	58	8
	27	9.0	2.6	....	12	4	..	12.5	4	21	65	10
	44	8.9	2.6	....	7.3	2	..	6.5	9	39	47	5
	49	8.1	2.3	....	7.4	1	..	6.7	20	43	30	7
	2 mo.	9.7	3.5	....	..	1	..	11.5	3	37	54	6
	3 mo.	13.5	4.8	....	0.5	..	..	8.3	3	30	57	10
	6 mo.	13.4	5.3	7.46	..	..	..	9.6	..	28	65	7
	11 mo.	13.5	5.7	....	..	..	..	10.5	1	32	59	8
Case 2: R. M.	10	3.1	0.78	8.77	6.4	22	4	26.0	24.6	35	32.9	7.5
Case 3: M. S. M.	3	8.3	2.2	8.57	..	22	2	11.8	12	38	38	12
	4	10.0	2.9	....	..	Occ.	..	12.0	..	..	..	..
	7	10.0	3.4	....	..	1	..	11.6	4	23	61	12
	9	10.6	3.6	....	..	Rare	..	10.2	..	..	..	..
	12	11.0	3.5	....	..	..	..	10.2	..	..	..	..
	17	11.8	3.7	....	0.4	..	..	15.5	2	38	49	11
	2 mo.	12.4	4.0	7.99	..	Rare	..	16.5	1	24	69	6

* Age is given in number of days except when otherwise indicated.

Numerous erythroblasts and leukoblasts were present. Mitotic figures were fairly numerous (fig. 1 *C*). No phagocytes containing erythrocytes were found.

The last examination of the patient was on Nov. 30, 1936, when she was 1 year of age. Results of the physical examination and of the examination of the blood were normal. The gastric analysis showed normal acidity. At this time also an analysis of the gastric contents of the older brother, who apparently had had anemia in infancy, showed acid to be present.

CASE 2.—R. M., a boy, was born on Jan. 1, 1934, and died on January 10. His father was 33 years old and his mother 30; both were in good health. He had one brother, aged 7, who was in good health. There were no children dead; the period of gestation and delivery was not remarkable in any way, and the mother's Wassermann reaction was negative. The child's weight at birth was 6 pounds, ½ ounce (2,736 Gm.).

13. Footnote deleted by author.

Within twenty-four hours after the child was born, icterus appeared. It gradually increased for a few days but then abated somewhat. The baby nursed well, and its color did not attract particular attention until the tenth day, when an examination showed yellowish gray pallor of the skin and of the mucous membranes and when the spleen was found palpable. Even on that day the child's cry was strong.

The results of the blood count on the tenth day, the day of death, are shown in the table. (See also figure 2.) Polychromasia, anisocytosis, poikilocytosis and some stippling of red cells were noted. Megaloblasts with mitotic figures were fairly numerous. Many atypical monocytes were seen, some of which had vacuoles

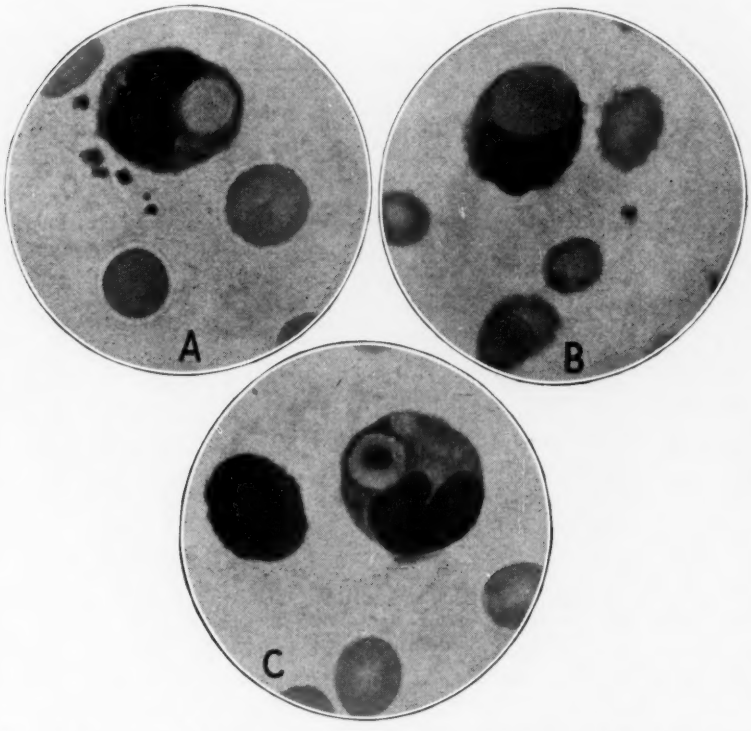

Fig. 2 (case 2).—*A*, blood smear (× 1,200, Wright stain) which shows a phagocyte containing a clear unstained space about the size of an erythrocyte. *B*, blood smear (× 1,200, Wright stain) of a phagocyte containing an erythrocyte with stained hemoglobin. *C*, blood smear (× 1,200, Wright stain) showing, at the right, a phagocyte containing a large circular space with dark material in the center suggesting the remains of an erythroblast; at the left, a megaloblast is seen.

and were similar to those in case 1. The icteric index was 50. The result of the fragility test was not definitely abnormal, but there was a suggestion of increased resistance to the hypotonic saline solutions. An intramuscular injection of whole blood was given on the day of death, about twelve hours before the first blood count was taken.

Autopsy.—Gross examination disclosed an extreme, faintly yellowish pallor of the entire skin surface and of the mucous membranes. All of the viscera showed pallor. The spleen was distinctly enlarged, weighing approximately 60 Gm. On section, it appeared dark reddish gray and friable. Bone marrow of the head of the sternum and of the right femur was scanty and rather pale grayish red. Microscopic examination showed a slight fatty degeneration of the myocardium and slight bronchopneumonia in relatively small areas, with the presence in

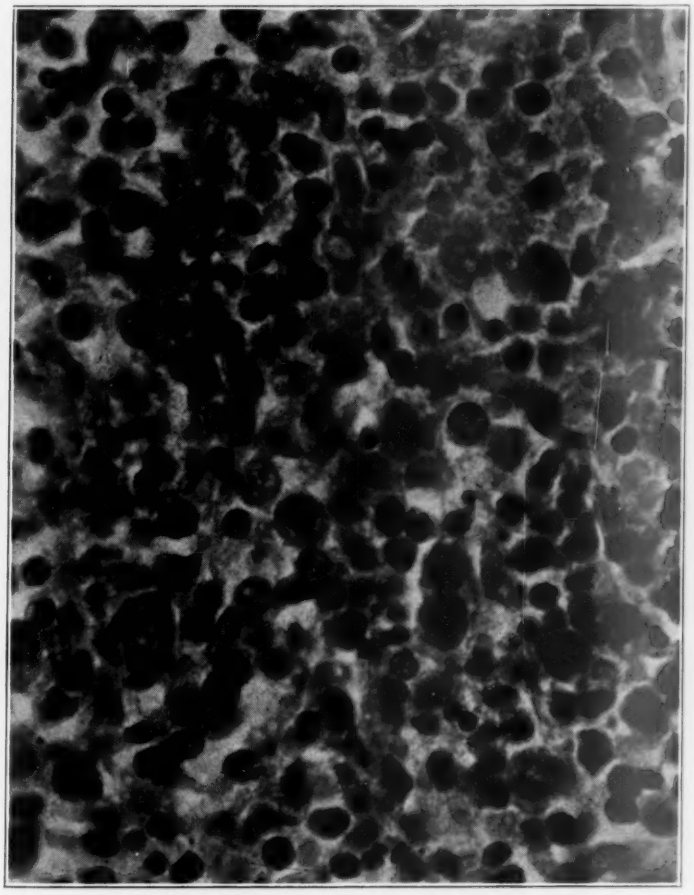

Fig. 3 (case 2).—Section of the spleen (× 750) showing numerous scattered myeloid cells. The yellowish granular pigment present does not show clearly in the photomicrograph.

certain places of what appeared to be keratinized epidermis, probably from aspirated amniotic fluid. There was myeloid activity in the spleen (fig. 3), with a considerable amount of scattered yellowish granular pigment, found largely in mononuclear cells. Moderate hyperplasia, involving both leukoblastic and erythroblastic elements, was seen in the bone marrow (fig. 4), and a very few small scattered myeloid cell groups were discovered in the liver.

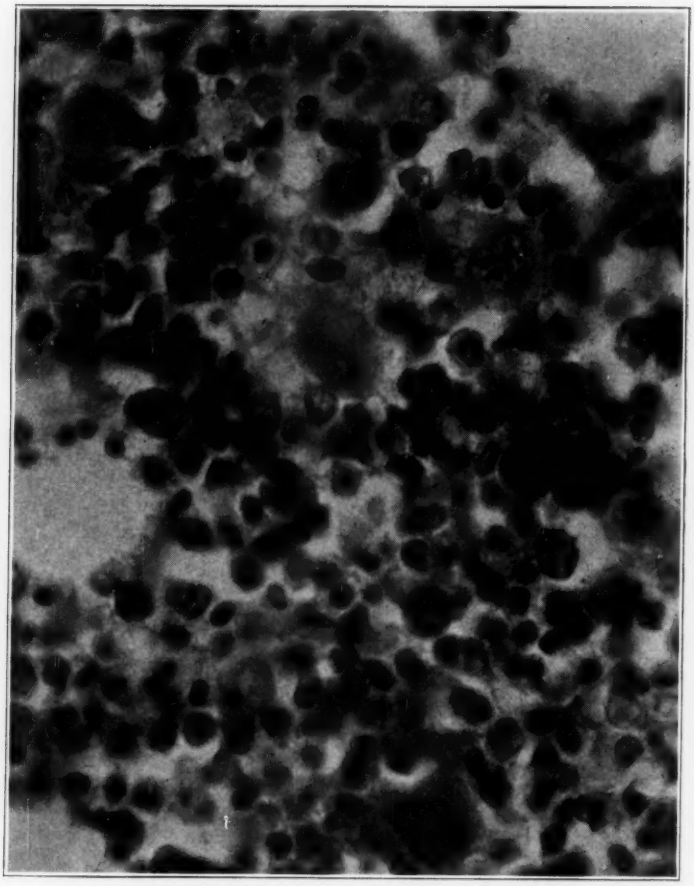

Fig. 4 (case 2).—Section of bone marrow (× 750) showing the degree of activity of the leukoblastic and the erythroblastic element. Several megakaryocytes are seen.

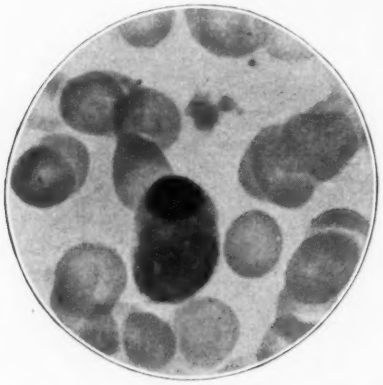

Fig. 5 (case 3).—Blood smear (× 1,200, Groat-Jenner stain), showing a phagocyte which contains a nucleus resembling that of an erythroblast.

CASE 3.—M. S. M., a girl, was born Feb. 8, 1937. Delivery was not unusual, but the mother, who was a nurse, continued her work up to two or three days before delivery and concealed her pregnancy by limiting her diet to the point where she gained only about 6 pounds (2.7 Kg.). The baby's weight was 6 pounds, 7 ounces (2,920 Gm.). The mother's color was rather poor during the latter part of pregnancy, her first, but no examination of the blood was made.

On the second day of life, the baby was pale and slightly icteric. The icterus increased rapidly in the next twenty-four hours. The blood count is given in the table. Megaloblasts and mitotic figures were rare. Two erythrophagocytes were found, one containing pinkish débris, and a somewhat degenerated mass suggestive of a remnant of a partially "digested" nucleus; the other containing a dense nucleus which resembled that of an erythroblast, although no surrounding hemoglobin was seen (fig. 5). There were, however, other monocytes which contained clear round spaces the size of erythrocytes or smaller.

A transfusion was done on the third day of life. The baby's progress was satisfactory, and at the present time she appears to be normal in every way.

COMMENT

Although the reports of erythrophagocytosis in infants are rare, we think that the phenomenon may not be uncommon in anemia of infancy. The phagocytes in our 3 cases were not numerous and could easily have been overlooked had not the smears been searched with the low power objective to pick out cells which, by their characteristically irregular outline and light circular cytoplasmic areas, seemed to include extraneous matter. Our second case was interesting in this connection, because the phagocytosis was found only on reexamination of the smears two years later, after our interest in the subject had been aroused by the first case. In Abt's case the erythrophagocytes must have been found more readily, for they were present in numbers as high as 5 per hundred leukocytes.

In addition to the cells containing definitely stained erythrocytes, in all 3 cases there were also numerous monocytes which contained one or more possible vacuoles the size of erythrocytes or smaller (fig. 2*A*).

In each case a nucleated red cell was found within a phagocyte (fig. 1*B*, 2*C* and 5). Although the nuclei resembled those of erythroblasts, there is a possibility that they might have been lymphocytic nuclei, since phagocytosis of lymphocytes is frequently observed in tissues.

As to the type of the phagocytic cells, we feel that in all 3 cases they belonged in the monocytic group.

It hardly seems reasonable that the small number of erythrocytes found in phagocytes is important in the production of such severe anemia as these babies showed. Such phagocytic activity, however, suggests a fundamental variation from the normal on the part of either the circulating phagocytes or the erythrocytes. There is the possibility that the erythrophagocytosis is due to a functional abnormality of

certain monocytic cells amounting to an unusual phagocytic activity toward particulate matter. Similar erythrophagocytic cells have been found in the circulating blood in myeloblastic and monocytic leukemia.[14]

If the phagocytosis results from an abnormality of the erythrocytes, there is no evidence to show whether the abnormality is due to faulty genesis, to injury of previously normal cells or to both. It is not likely that in our cases the cells ingested were foreign,[15] unless from placental hemorrhage, for in 2 of the 3 instances the phagocytosis was manifest before blood was administered. In case 2, a small intramuscular injection of blood was given twelve hours before the count was made. The fact that erythrophagocytosis has been found in the circulating blood in pernicious anemia [11] might indicate that in certain instances the phenomenon is related to the developmental realm. Its presence in sickle cell anemia [16] also bears out this possible explanation.

On the other hand, the frequency with which the condition has been found in malaria [17] and in relapsing fever [17a] and also its occurrence in potassium chlorate poisoning,[18] in sepsis and infectious diseases,[11] in severe secondary anemia,[11] in paroxysmal hemoglobinuria and in poisoning by mushrooms and by ether extract of male fern [19] suggest that injury of the cells may be important.

It is a striking fact that the appearance of the erythrophagocytes in our case 1 and in Abt's case was transitory and coincided with the period of severest anemia, leukocytosis and erythroblastosis. In Abt's case the first examination of the blood was on the ninth day of life, and the erythrophagocytes were found on that day and until the fifteenth day of life. Our first examination in case 1 was on the eleventh day of life, and the phagocytes were present from that day until the twentieth

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14. Bowcock, H., and Bishop, E. L.: A Case of Acute Leukemia with Unusual Cell Forms in the Blood, Ann. Int. Med. **3**:1252 (June) 1930. Kato, K.: Hematology and Pathology of Leucemic Reticuloendotheliosis [fig. 3], J. Pediat. **8**: 679 (June) 1936. Abt.[11]

15. Hanau, G.: Erythrophagia, Gazz. d. osp. **55**:1061 (Sept.) 1934. Engelbreth-Holm, J.: Zwei Fälle von Erythrophagie im zirkulierenden Blut, Klin. Wchnschr. **13**:728 (May 19) 1934.

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17. (*a*) Hung, S. L.: Ueber die Erythrophagozytose durch Monozyten und Lymphozyten im peripheren Blut bei Febris rekurrens und Malaria, Arch. f. Schiffs- u. Tropen-Hyg. **40**:17 (Jan.) 1936. (*b*) Connal.[10]

18. Lange, F.: Ueber einige bei einer Kali-Chloricum-Vergiftung erhobene Blutbefunde, Med. Klin. **5**:1929, 1909.

19. Sabrazès, J.: Signification pathologique des formes anormales des globules blancs du sang, Gaz. hebd. d. sc. méd. de Bordeaux **43**:481, 1922; Presse méd. **30**:868 and 911, 1922; Arch. d. mal. du cœur **16**:41 (Jan.) 1923; in supplement to Rapports du Congrès français de médecine, Paris, 1922.

day. In case 2 the only examination was on the tenth day, the day of death. In case 3 the anemia had developed by the second day of life, and although in the first count, taken on the third day, only one phagocyte which contained definitely stained hemoglobin was found; others with large vacuoles were present and also one containing a nucleated cell, possibly an erythroblast. Blood transfusion was done early in this case (third day), and improvement was noted at once. It is also interesting that in case 1 erythrophagocytosis and anemia preceded any abnormal erythroblastosis, as shown in the first count. The erythroblasts were numerous, however, on the next day, continued to increase in number over a period of a week and then gradually decreased after the phagocytes had disappeared.

SUMMARY

Three cases of anemia of the newborn are added to the other 70 or so instances reported in the literature.

Blood smears from 2 of the 3 infants showed definite evidence of phagocytosis of erythrocytes by a monocytic type of cell. In the third case, in which the patient was seen earlier after birth than in the other 2, some evidence of erythrophagocytosis was present.

In the literature, this condition in infants, other than those with malaria, has been mentioned previously in only 4 instances, namely, in cases of anemia or of icterus of the newborn. The 3 cases reviewed here bring the number to 7.

This phagocytic activity suggests a fundamental variation from the normal on the part of either the monocytes or the erythrocytes.

ENCEPHALOGRAPHY IN RAPIDLY PROGRESSING CEREBRAL ATROPHY DUE TO TRAUMA

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Cortical atrophy is due to a disturbance in the cerebrospinal fluid–eliminating mechanism, which permits an increase in the amount of supracortical fluid with varying degrees of pressure. The factors which may cause the pathologic intracranial condition are many: encephalitis following measles, chickenpox or whooping cough; congenital malformation of the brain; congenital internal hydrocephalus; tumor of the brain; meningitis, or trauma. The first response of the brain to edema is an accumulation of fluid with resulting pressure and progressive atrophy and dilatation of the ventricles or the accessory channels. Obstruction at any point causes dilatation of the ventricular system and cortical shrinkage.

The rapidity with which cortical atrophy may develop is strikingly illustrated in the following case, in which trauma was the only etiologic factor discovered. The condition gave rise to a syndrome similar to that seen in cerebral lesions due to infection or in congenital malformations of the brain.

REPORT OF A CASE

G. E., a girl 18 months old, was admitted to the hospital April 4, 1934. Six days before entry, the baby fell from her carriage onto a granolithic sidewalk. The fall resulted in laceration and ecchymosis of the forehead above the right eye. The infant appeared to be normal for three days after the accident, but then lapsed into unconsciousness. Since there was no change in her condition for the next three days, she was referred to the pediatric department of the hospital.

Examination.—On admission examination of the eyes revealed no exudates or hemorrhages. The pupils were equal and regular and reacted to light and in accommodation as well as consensually. The corneas and maculas were clear. The disks were not elevated. Over the right eye there was an uninfected laceration which had almost healed. In other respects, the general physical examination gave negative results. The child was still in a comatose condition. The rectal temperature was 100.4 F., the pulse rate between 120 and 140 and the respiratory rate 30. Respirations were shallow, and the cry was weak and high pitched.

Roentgen examination performed an hour after admission showed no evidence of fracture or of other abnormality. Percussion of the skull at this time showed definite dulness in the right parietal region extending from above the right ear two thirds of the distance to the longitudinal suture, and from the temporal region posteriorly two thirds of the distance to the occiput.

Lumbar puncture yielded 20 cc. of clear fluid under slight pressure; no blood or xanthochromia was apparent. The spinal fluid showed a cell count of 3, all of

which were lymphocytes, a total protein content of 5 mg. per hundred cubic centimeters and a trace of globulin. The Kahn test of the fluid was negative. Examination of the blood revealed 5,910,000 erythrocytes, 6,300 leukocytes and 95 per cent hemoglobin. The differential count was 61 per cent neutrophils and 39 per cent small lymphocytes. The Kahn test of the blood was negative.

Course.—The following day the child held the arms and legs rigid and continued to cry at intervals, a long, high-pitched cry. A diagnosis of extradural hemorrhage was made. A second roentgenogram of the skull showed no change, although dulness to percussion in the right parietal region was more pronounced.

On April 9, five days after admission, a decompression was made over the right parietal area with the aid of procaine hydrochloride anesthesia. A small amount of serum escaped from between the dura and the calvarium. The dura was not opened, as there was no bulging or increased tension. The temperature rose to 104.4 F. and then quickly dropped to normal. Fluids were forced, and physiologic solution of sodium chloride was given subpectorally.

On April 14 an encephalogram was made; 100 cc. of cerebrospinal fluid was withdrawn by the lumbar route and replaced by air (fig. 1). The ventricles were

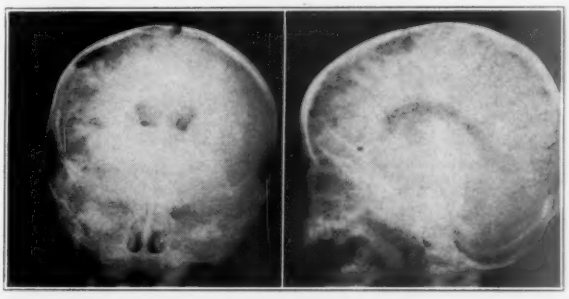

Fig. 1.—Encephalograms made April 14, 1934, showing the ventricular system to be normal.

fairly well filled and not deformed or displaced. The impression of the roentgenologist was that the ventricular system was normal. The child was extremely weak afterward. In a few days, however, she appeared more aware of her surroundings and took milk and cereal. Her temperature and pulse rate continued to be normal.

On April 23, nine days later and twenty-five days after the injury, a second encephalogram was made (fig. 2). A small amount of air was visible over the right cortex, suggestive of progressive atrophy of the right hemisphere. The anterior horn of the right lateral ventricle was dilated and somewhat displaced to the right. The observations suggested a progressive arachnoiditis that was producing an early hydrocephalus.

The fundi of the eyes were still normal. The condition of the patient remained about the same. A third encephalogram made May 28, two months after the injury, revealed more extensive dilatation of the ventricular system (fig. 3). The position of the ventricles again appeared normal, and there was no displacement from the midline. There was marked dilatation of the right frontal horn, its wall being within 1 cm. of the anterior and lateral walls of the anterior cranial fossa.

In view of the progressive cortical destruction and of the impossibility of improvement, the patient was discharged June 5. The diagnosis was injury of the head with resultant edema of the brain and progressive cortical destruction.

Fourteen months after the onset of symptoms, on June 19, 1935, the child was readmitted. During the interval her general physical condition had shown a slight improvement, but her mentality had been definitely retarded She had cried most of the time and had frequently vomited undigested food and mucus.

Examination of the blood revealed 3,820,000 erythrocytes, 6,100 leukocytes and 70 per cent hemoglobin. The differential count showed 54 per cent neutrophils, 44 per cent small lymphocytes, 1 per cent eosinophils and 1 per cent basophils.

Fig. 2.—Encephalograms made April 23, nine days after those of figure 1, showing the progressive atrophy of the right hemisphere and the dilatation of the anterior horn of the right lateral ventricle.

Fig. 3.—Encephalograms of May 28, showing extensive dilatation of the ventricular system, especially of the right frontal horn, and the rapid progress of the atrophy in only thirty-five days.

On June 21 a fourth examination of the brain with encephalograms, for which approximately 120 cc. of spinal fluid had been replaced by air, showed no change in the appearance of the ventricular system except for further dilatation of the anterior portion of the right frontal horn (fig. 4). The latter now measured about 4 cm. in diameter, with its anterior wall within about 1 cm. of the inner table of the frontal bone. There was still no lateral displacement of the ventricular system.

The following morning the patient was restless; her pulse soon became intermittent and of poor quality. In spite of the administration of epinephrine, caffeine and oxygen, she failed to rally and died at noon. Permission was obtained for a postmortem examination.

Autopsy.—After fixation the brain was sectioned coronally. The ventricles were dilated, especially the anterior horn of the right lateral ventricle. This was enlarged to such a degree that the brain tissue measured only 4 mm. in thickness. The convolutions were ironed out over this lobe, but were still visible. There was no evidence of old exudate, either internal or external. The ventricular system was patent throughout and showed no obvious pathologic condition. The exact cause of death was uncertain; except for revealing Meckel's diverticulum, the remainder of the pathologic examination gave negative results.

The histologic impression was that there were internal, asymmetric hydrocephalus of the anterior horn of the right ventricle following trauma, and cortical atrophy.

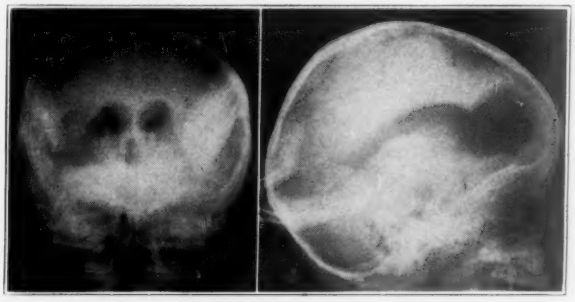

Fig. 4.—Encephalograms made June 21, 1935, almost fourteen months after the onset of symptoms, showing further dilatation of the anterior portion of the right frontal horn.

COMMENT

The observations in this case demonstrate the definite value of encephalography in determining the location and extent of intracranial damage. The rapidity with which edema of the brain with progressive atrophy and dilatation of the ventricles developed is shown especially in the series of the first three encephalograms made April 14, April 23 and May 28, over a period of only six weeks. The condition revealed by encephalography was later confirmed by postmortem examination.

Although the reaction of the patient to encephalography is sometimes severe, young children tolerate the procedure rather well, and symptoms of bradycardia and shallow respiration usually disappear in a day or two. In dealing with lesions of the brain, the use of encephalography to arrive at a more accurate prognosis, by appraisal of anatomic cranial defects, is recommended.

150 Purchase Street.

PAROXYSMAL NODAL TACHYCARDIA TREATED WITH MECHOLYL

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The occurrence of paroxysmal tachycardia in children is rare, as Taran and Jennings [1] found from a recent survey of the literature. The treatment for this disorder was frequently uncertain until Starr [2] worked out a technic which, by the use of acetylbetamethylcholine chloride (mecholyl), was effective in terminating 90 per cent of acute paroxysms in adults. The case described below is of interest because the victim was a child and the attacks were frequently repeated and because mecholyl, when used in adequate dosage, was invariably effective.

REPORT OF A CASE

A Jewish girl of 6 years came to the Babies Hospital on March 8, 1936, because of an excessively rapid heart action. During her life she had eight similar attacks, lasting from two to fourteen days each. The first of these occurred when she was 9 months old. At the time of its inception she had been riding in a closed automobile, and it was thought that the fumes were responsible for her symptoms. Vomiting ushered in the attack and continued intermittently for the next twelve hours. Later, the mother noted violent pulsation of the anterior wall of the chest, and a physician who was summoned stated that the heart rate was 220 per minute. Vomiting ceased after twelve hours, but the infant remained weak until the heart rate abruptly returned to normal three days later, after which she gained rapidly in strength and appetite.

The second attack occurred during the course of an infection of the upper respiratory tract with associated cervical adenitis when the girl was 2½ years old. This attack lasted for two days and was not accompanied by any symptoms other than the tachycardia. At 3½ years, the child had a similar episode during a cold with cervical adenitis. On this occasion the paroxysm persisted for two weeks and made her weak. After her fourth birthday party, she had a bout that lasted two days. At 4½ years, a similar episode followed excitement, and again at 5 years the same train of events took place. At 5¾ years another attack of two days' duration occurred, apparently without inciting cause.

The child's most severe seizure occurred in January 1936, about two months before she came to the Babies Hospital. There was no apparent cause. On the third day of tachycardia, the girl lost consciousness and was taken to a hospital in

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From the Department of Diseases of Children of the College of Physicians and Surgeons, Columbia University, and the Babies Hospital.

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the neighborhood, where she remained for nine days. Enlargement of the liver and chronic tonsillitis were reported to the parents at this time.

On March 6, 1936, the girl ate a heavy evening meal and later complained of sore throat, and on the following morning her heart was seen to be beating rapidly again.

All of the paroxysms started and stopped abruptly. The child's appetite usually failed during periods of tachycardia, while in the intervals she seemed perfectly well in every respect. She had never had any symptoms suggestive of rheumatic fever, cyanosis, edema, tremor, unusual perspiration or exophthalmos. Attempts had been made during the more recent attacks to slow the heart with digitalis, but details of the dosage were not known to the parents. For the year preceding admission, her exercise had been limited and she had been carried upstairs by her mother.

The details of the girl's history gave no clue to the nature of the presenting symptom. One grandparent had died of disease of the kidneys, and another was suffering from diabetes mellitus. Both parents and two older sisters enjoyed good health. The patient's birth was a spontaneous, easy delivery at full term. Pregnancy was complicated by the fact that the mother had a "nervous breakdown" lasting from the sixth month of gestation until parturition. The infant took the breast well and was not weaned until she was 11 months old. She received orange juice at 2 months, viosterol at 3 months and solid foods at 4 months. Dentition did not start until 12 months, but her physical and mental development was otherwise normal. She was vaccinated unsuccessfully on three different occasions. Diphtheria toxin-antitoxin was administered at 2 years. Aside from the illnesses noted above, she had never been sick.

Examination.—At the time of the first admission to the Babies Hospital, the patient was a moderately obese girl who did not appear ill. The temperature was 99.4 F., the pulse rate 200 and the respiratory rate 28. She was quiet, friendly, cooperative and without any subjective complaints. There was no orthopnea, dyspnea or cyanosis. The pupils reacted well to light; the extraocular movements were well performed, and there was no evidence of exophthalmos or poor convergence. There was no acute inflammation of the tympanic membranes, the nasal mucosa or the pharyngeal mucosa. The teeth were in good condition. Tonsils were of moderate size without evidence of infection. The thyroid gland and lymph nodes of the cervical region were of average size.

The chest was barrel shaped and expanded well with respirations, and the lungs were clear on percussion and auscultation. The maximum impulse of the heart could be seen and felt in the fourth left interspace just below the nipple. The cardiac sounds were rapid and regular and did not vary with respiration or with pressure over the carotid sinus. No murmurs were heard. No enlargement of the cardiac borders could be determined by percussion. The peripheral pulses were rapid and of small volume. It was not possible to record the blood pressure.

The abdomen was obese, relaxed and devoid of palpable masses or organs. The genitalia were normal. There was no cyanosis, edema or clubbing of the digits. Neurologic examination revealed no abnormal signs. The patient complained slightly of being cold when exposed for examination, although the room was well heated.

Laboratory Studies.—Results of the blood count were as follows: hemoglobin, 14.6 Gm. per hundred cubic centimeters; erythrocytes, 5,100,000 per cubic millimeter; leukocytes, 8,200 per cubic millimeter; polymorphonuclears, 64 per cent and lymphocytes, 34 per cent. The urinalysis showed a neutral reaction, a specific

gravity of 1.010, a trace of albumin and no sugar, acetone or diacetic acid. Results of the microscopic examination were negative. The erythrocyte sedimentation rate was 5 mm. in one-half hour and 15 mm. in one hour. The Mantoux test gave a negative reaction to 0.1 mg. The Kahn test gave a negative reaction. The electrocardiogram showed a ventricular rate of 210, the rhythm originating in the auricle close to the auriculoventricular node. The T wave was diphasic in leads I and II and inverted in leads III and IV (fig. 1). No P waves were visible.

Course.—A diagnosis of paroxysmal nodal tachycardia was made from the data thus acquired. Pressure over the carotid sinus was tried without result. A sub-

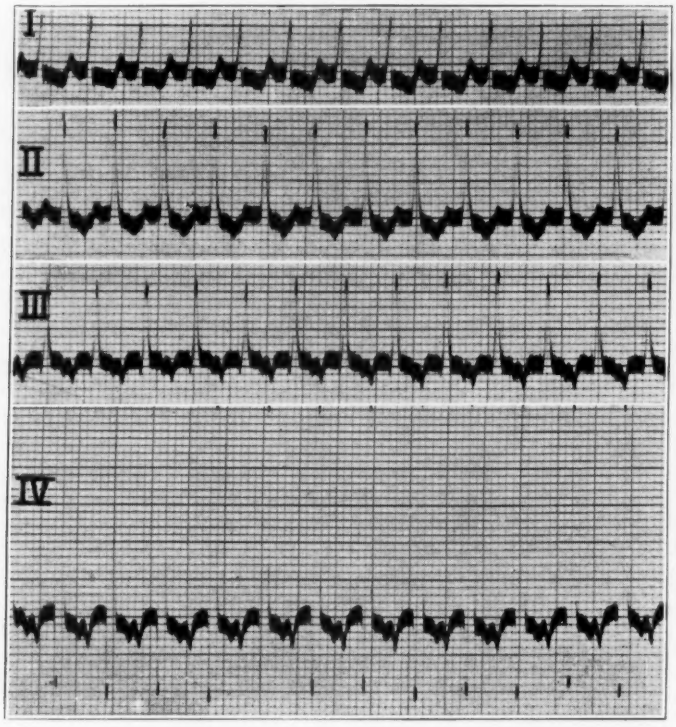

Fig. 1.—Electrocardiogram taken during the height of a paroxysm.

cutaneous injection of 5 mg. of mecholyl was then given and continuous auscultation of the precordium carried out. Within two minutes after administration of the drug, the patient had a sense of constriction in her throat, which increased in severity and which was followed by precordial oppression and by difficulty in breathing. Flushing of the face and neck with diaphoresis and nausea followed. About four minutes after the injection, the heart beat became slower and irregular, and it finally stopped for two or three seconds. The sounds then returned feeble and irregular, but gradually they increased in intensity, until a normal regular rhythm at a rate of 120 beats per minute was established. As soon as asystole occurred, the patient was given 0.3 mg. of atropine sulfate by hypodermic injection. Within a minute all the uncomfortable sensations began to subside, and fifteen minutes after she received the mecholyl she was feeling comfortable, though a little weak.

An electrocardiogram taken on the following day showed a sinus tachycardia with a ventricular rate of 110. The PR interval was now 0.13 second, the Q wave in lead III was prominent and all the T waves were upright (fig. 2). For the next four days the pulse rate varied between 90 and 100, and the blood pressure was obtained at 120 systolic and 70 diastolic. The patient was discharged as cured six days after admission.

Since this original visit to the Babies Hospital the patient has suffered seventeen more paroxysms severe enough to require medical attention. The pertinent facts concerning her twenty-six major attacks are listed in table 1. Although a few of the paroxysms seemed to be precipitated by infections of the upper part of the respiratory tract, by unusual exercise or by excitement, the majority occurred without recognizable cause.

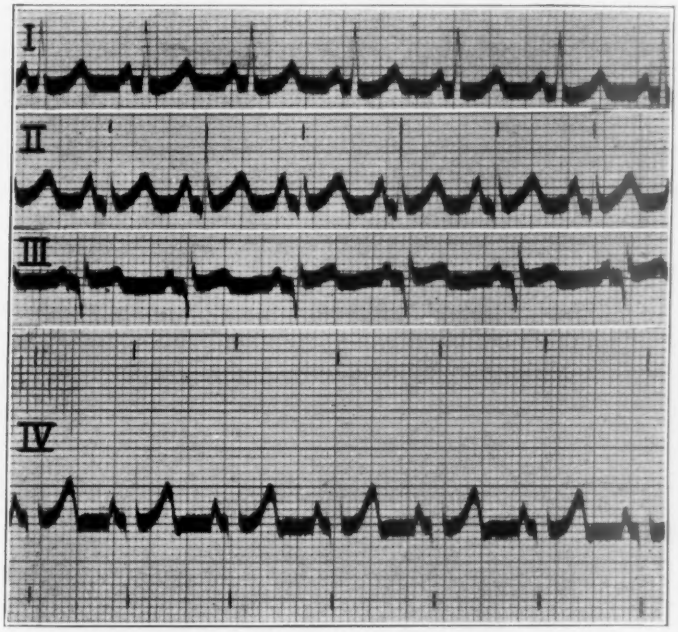

Fig. 2.—Electrocardiogram taken on the day after the termination of a paroxysm.

Before resorting to mecholyl, attempts were usually made to slow the heart rate by other means. At one time or another pressure over the carotid sinus, lateral compression of the chest, pressure over the eye, ipecac, mechanical induction of vomiting, breath holding, slapping of the precordium, holding the patient inverted for several minutes and having her swallow large boluses of food were tried without effect. Pressure over the carotid sinus and the inverted position each produced transient slowing of the heart rate on one occasion, but never succeeded in reverting the heart to its normal rhythm.

Termination of the paroxysm within fifteen minutes was accomplished by mecholyl in fourteen of the seventeen later episodes. The doses used ranged from 10 to 100 mg. and were occasionally given in two or more portions. In three instances resumption of normal rhythm could not be attributed to mecholyl. Twice

the patient had a remission due either to slight surprise or to the realization that a subcutaneous injection was imminent. In the third instance small doses of the drug were given unsuccessfully on two occasions, followed several hours later by a spontaneous remission. Insufficient dosage produced the usual side effects.

The response to mecholyl was always similar to that described. Although the production of brief asystole was disquieting at first, confidence in the safety of the drug was gained through repeated usage and through the ease with which the side effects could be controlled by atropine. Once an erroneous dose of 100 mg. was given with striking, but not alarming, results. Asystole occurred after forty seconds, lasted for about ten seconds and was followed by several minutes of bradycardia.

Attempts to prevent further paroxysms through the use of drugs were conspicuously unsuccessful. Quinidine in daily doses of 3 grains (0.19 Gm.) was

TABLE 1.—*Record of Major Paroxysms of Tachycardia*

No.	Date	Age	Duration	Treatment	Comment
1	.....	9 mo.	3 days	None	Riding in a closed car
2	.....	2½ yr.	2 days	None	Cervical adenitis
3	.....	3½ yr.	14 days	None	Cervical adenitis
4	.....	4 yr.	2 days	None	Birthday party
5	.....	4½ yr.	2 days	None	Excitement
6	.....	5 yr.	2 days	None	Excitement
7	9/../35	5¾ yr.	2 days	None	
8	1/../36	6 yr.	12 days	?	Hospitalized
9	3/ 6/36	6 yr.	4 days	5 mg. mecholyl	Pharyngitis
10	6/ 2/36	6½ yr.	3 days	4-5-10 mg. mecholyl	Spontaneous remission after failure of drug
11	6/11/36	6½ yr.	1 day	10 mg. mecholyl	
12	5/15/37	7½ yr.	6 days	7.5-5 mg. mecholyl	
13	6/ 9/37	7½ yr.	1 day	7-5 mg. mecholyl	Given by family doctor with temporary effect
14	6/10/37	7½ yr.	1 day	12-20-5 mg. mecholyl	Quinidine and belladonna started
15	7/ 1/37	7½ yr.	7 days	15 mg. mecholyl	
16	8/ 6/37	7½ yr.	1 day	100 mg. mecholyl	
17	8/21/37	7½ yr.	2 days	16 mg. mecholyl	
18	9/14/37	7½ yr.	2 days	15-10 mg. mecholyl	
19	9/26/37	7½ yr.	2 days	25-10-10 mg. mecholyl	Exciting moving picture
20	10/ 2/37	7½ yr.	1 day	40 mg. mecholyl	Quinidine and belladonna stopped; digitalis begun
21	10/15/37	7½ yr.	1 day	40 mg. mecholyl	Digitalis stopped; convalescent home
22	2/15/38	8 yr.	1 day	40 mg. mecholyl	Strenuous walk
23	3/ 5/38	8 yr.	1 day	Spontaneous remission	
24	3/14/38	8 yr.	1 day	Spontaneous remission	
25	3/21/38	8 yr.	1 day	40 mg. mecholyl	Overexertion
26	4/ 7/38	8 yr.	1 day	40 mg. mecholyl	

given for a period of four months. Belladonna in small daily doses was also tried. On one occasion the child was digitalized. If any result was obtained from these procedures, it was an increase in the frequency of paroxyms and an increase in the tolerance of the patient for mecholyl. Greater success was obtained by placing her on a regimen of limited exercise in a convalescent home for four months. During this time she remained free of attacks. When she was returned to her home, though exercise was limited, the attacks recurred.

Evidence of disturbances of myocardial function were apparent both during and immediately after paroxysms. In general, the longer the paroxysms lasted, the more pronounced such phenomena became. The pulse rate during an attack was always over 200 per minute and could not be counted at the wrist because of small volume. Readings of the blood pressure were frequently unobtainable and were always low. Dyspnea and mild orthopnea were usually present. The girl's desire and ability to exercise were distinctly curtailed. Hepatic engorgement, dependent edema and rales at the bases of the lungs were not encountered. After

one long paroxysm, however, cyanosis was observed, the heart showed slight enlargement on percussion, and a roentgenogram of the chest revealed an abnormal prominence of the left cardiac border, although the total transverse diameter was not increased. In this film also an increase in the bronchovascular markings suggested the presence of pulmonary congestion.

On three occasions the circulation time was measured by the intravenous injection of saccharin during and after an attack. In each instance an abnormally long time was recorded at first (fifty-seven, twenty-three, twenty-six seconds), with a dramatic fall to normal levels (sixteen, eight, nine seconds) after a remission had been obtained. Measurements of venous pressure under the same circumstances failed to disclose any consistent alteration. None of the readings made during the course of a paroxysm was pathologically elevated.

Electrocardiograms taken during the height of tachycardia were invariably similar to those of figure 1. Tracings made after the termination of a paroxysm occasionally showed notched P waves, flat or inverted T waves and once an elevated RT interval. Left preponderance was constantly observed. These

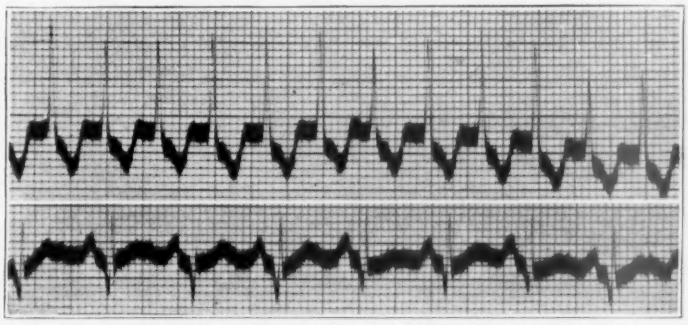

Fig. 3.—Portions of a continuous electrocardiographic tracing during the administration of mecholyl. The second tracing follows the period of asystole closely (lead II).

abnormalities were interpreted as evidence of damage to the cardiac muscle. All of the abnormalities except the preponderance on the left disappeared during the four month period of freedom from attacks. Figure 3 shows portions of a continuous tracing made during the action of mecholyl.

The basal metabolic rate was measured at + 8.9 per cent after recovery from a paroxysm.

COMMENT

The infrequency of paroxysmal tachycardia in children is attested by a survey of the literature made by Taran and Jennings,[1] who could discover only 52 cases reported in patients under 15 years from 1892 to 1935. This figure included all types of rapid, regular heart beats. In only 22 cases was there evidence definite enough to exclude auricular flutter. The experience of the Babies Hospital is in accord with this observation, since only 2 of more than 60,000 patients admitted have received this diagnosis. (The other patient was also successfully treated with mecholyl.)

Although recurrence of attacks is common in adults, the occurrence of at least twenty-six major paroxysms in this child over a period of eight years is noteworthy.

The center of the disorder is an ectopic, irritable focus in the myocardium which gains control of the conducting mechanism and sets up a rapid but regular cardiac rate. The focus usually lies in the auricle but may also be in the ventricle or atrioventricular node. Rational attempts to stop paroxysms have been directed toward the production of a strong vagal stimulus sufficient to slow the heart rate and allow the sinoauricular node to regain control of the conducting mechanism. In some instances this may be accomplished by pressure on the eyeballs or on the carotid sinus or by the induction of vomiting. Patients frequently learn to use such methods to control their attacks. Dale [3] concluded that when the vagus nerve was stimulated, acetylcholine was liberated at the nerve endings and acted as an intermediary between nerve and muscle. Intravenous injections of this substance have been used with limited success in terminating paroxysms of tachycardia. Hydrolysis takes place so rapidly in the blood stream that a prolonged effect cannot be obtained. More consistent success has been attained by Starr [2] with a modification of acetylcholine, namely acetylbetamethylcholine chloride, or mecholyl. He was successful in controlling 90 per cent of the paroxysms in a large series of cases. All the patients were adults, and doses averaged 30 mg. In some instances the original dose had to be supplemented with pressure of the carotid sinus or with another, smaller injection of mecholyl. Starr warned against intravenous use of the drug because of the production of prolonged asystole; he pointed out, however, that there is a good margin of safety, since its effects can be quickly neutralized by atropine and since continued vagal stimulation in animals will not produce permanent cardiac arrest, as the heart eventually escapes and assumes a normal rhythm.

The case described here confirms Starr's experience in the use of mecholyl. Of sixteen trials, fifteen were immediately successful. The side reactions were frequently severe but could be well controlled with atropine. Doses ranged from 5 to 40 mg., and on several occasions more than one dose was required. The safety of the drug was attested by the fact that the prompt response to an erroneous dose of 100 mg. was not harmful.

Recognition of the factors which precipitate paroxysms is essential before an adequate attempt can be made to forestall them. The etiologic agents which have been accused in this disease are legion: organic disease and congenital malformation of the heart, several of the acute infec-

3. Dale, H. H.: Croonian Lectures on Some Chemical Factors in Control of Circulation, Lancet **1**:1285, 1929.

tious diseases, food allergy, tumors of the myocardium, hyperthyroidism and psychic and emotional factors. In the case described here emotional factors most frequently preceded the onset of the paroxysms and apparently caused them. Further support of this belief is added by the fact that she was free of attacks during the four month period away from home. Clinical and laboratory examinations have consistently failed to reveal any organic heart disease or the presence of thyrotoxicosis.

The use of quinine, of quinidine and of digitalis has not generally met with success [4] in preventing the recurrence of paroxysms. These drugs depress the irritability of the auricle and increase conduction time. In this patient they not only were useless but actually seemed to increase the frequency of attacks. In addition, as noted by Starr,[2] larger doses of mecholyl were required when the patient was under the influence of quinidine.

Signs and symptoms of myocardial failure have been described during prolonged paroxysms.[5] Dilatation of the heart generally appears first and the circulation time is prolonged; later, enlargement of the liver, cyanosis, peripheral edema and a fall in arterial blood pressure may occur. Such phenomena, with the attendant risk of permanent myocardial damage, should be prevented whenever possible.

SUMMARY

A case of repeated episodes of paroxysmal tachycardia in a girl of 8 years is reported.

No clear etiologic agent could be demonstrated, but emotional factors were frequently present.

4. Weiss, S., and Sprague, H. B.: Vagal Reflex Irritability and the Treatment of Paroxysmal Auricular Tachycardia with Ipecac, Am. J. M. Sc. **194**:53, 1937. Starr.[2]

5. Kahlstorf, A.: Das Verhalten der Herzgrösse beim Herzjagen, Klin. Wchnschr. **15**:1028, 1936. Stenhouse, A. B.: Paroxysmal Tachycardia Treated with Acetylcholine, Lancet **2**:1291, 1935. Taran and Jennings.[1] Weiss and Sprague.[4]

News and Comment

GENERAL

Physicians Certified by American Board of Pediatrics.—The following physicians have been certified by the American Board of Pediatrics since the last report:

Pat Bronstein, Chicago; Daniel Budson, Detroit; Vernon Richard DeYoung, Chicago; George L. Drennan, Jacksonville, Ill.; Joseph A. Gilmartin, Pittsburgh; Brenton M. Hamil, Detroit; Samuel J. Hoffman, Chicago; John L. Law, Ann Arbor, Mich.; Benjamin M. Levin, Chicago; George Calvert Malley, Zanesville, Ohio; Charles Miles McKinlay, Lexington, Ky.; Frederick William Munro, Detroit; Samuel J. Nichamin, Detroit; Mila I. Pierce, Evanston, Ill.; Joseph Nathan Rappaport, Evanston, Ill.; Walter J. Siemsen, Chicago; Ralph Spaeth, Chicago; M. I. Vinnecour, Chicago; Robert Breckinridge Warfield, Lexington, Ky.; Dwight Addison Weir, Mansfield, Ohio; Lawrence J. Wilhelmi, Joliet, Ill.; James L. Wilson, Detroit.

Harvey Society Lecture.—Dr. A. A. Weech, associate professor of diseases of children, College of Physicians and Surgeons, Columbia University, delivered the second Harvey Society Lecture on November 17. It was entitled "Significance of the Albumin Fraction of Serum."

American Board of Pediatrics.—The American Board of Pediatrics will hold examinations on November 14 and 15, 1939, in Cincinnati, preceding the annual meeting of the American Academy of Pediatrics. Appointments for this examination must be made before July 14, 1939.

PERSONAL NEWS

Dr. Black Appointed.—Dr. Robert A. Black, professor and head of the department of pediatrics, Loyola Medical School, has been appointed temporary president of the Board of Health of the City of Chicago.

DEATHS

The eminent Chilean pediatrician, Dr. Luis Calvo Mackenna, died in December 1937, after thirty years of untiring professional service. Professor Mackenna was the founder and first president of the Pediatric Society of Chile.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

CHLORIDE DEPLETION IN CONDITIONS OTHER THAN ADDISON'S DISEASE. A. W. WINKLER and O. F. CRANKSHAW, J. Clin. Investigation **17**:1 (Jan.) 1938.

Chronic depletion of the serum chloride was found in a group of patients with pulmonary tuberculosis, carcinoma of the lung and cardiac disease. These patients excreted chloride in the urine even when the serum chloride was reduced to a level at which excretion of chloride usually nearly ceases. This condition was not associated with recognizable disease of the adrenal glands or kidneys.

GUEST, Cincinnati.

INFLUENCE OF A DAILY SERVING OF SPINACH OR ITS EQUIVALENT IN OXALIC ACID UPON THE MINERAL UTILIZATION OF CHILDREN. P. BONNER, F. C. HUMMEL, M. F. BATES, J. HORTON, H. A. HUNSCHER and I. G. MACY, J. Pediat. **12**:188 (Feb.) 1938.

The high oxalic acid content in spinach as contrasted with some others of the leafy vegetables, together with the deleterious effect of this amount of oxalic acid on calcium metabolism in the rat, has renewed the interest in the consequence of the intake of this vegetable in the metabolism of man. The purpose of the present investigation has been to study the influence of a daily serving of 100 Gm. of puréed spinach (or its equivalent in oxalic acid) on the utilization of nitrogen, calcium and phosphorus in preadolescent children.

The authors made 121 metabolic balances for nitrogen, calcium and phosphorus on 10 growing children. The individual physiologic responses characteristic for each child on the different dietary regimens were determined for from sixty to eighty-five successive days by five day balance periods. Each child served as his own control. Control periods of twenty-five days on the ordinary mixed diet of common foods showed the children to be storing nitrogen, calcium and phosphorus. The storage rates were not significantly altered by the daily consumption of 100 Gm. of spinach; moreover, the variations were compatible with those normally observed in growth.

No cumulative toxic or other untoward effects could be determined either in the average daily retention or in the progressive storage curves of nitrogen, calcium and phosphorus during the period of consumption of spinach and oxalic acid or during the control period immediately following. The supplementing of an already adequate diet with a generous serving of spinach daily even for as long as forty consecutive days did not change the rate of storage of calcium in growing children when their intake of calcium was adequate to cover the precipitating effect of the oxalic acid and provide for the fluctuating needs of growth. The conclusion drawn from the data obtained is that in preadolescent children at least spinach is not harmful even in servings of 100 Gm. daily and that because of its richness in vitamins, minerals and iron it should retain its customary place along with other green leafy vegetables.

RAUH, Cincinnati.

NITROGEN RETENTION IN A CHILD DURING UNDERNUTRITION. E. S. CONN, Proc. Soc. Exper. Biol. & Med. **37**:496 (Dec.) 1937.

Marked underfeeding of an obese 10½ year old girl for eighty-five consecutive days, in spite of a decrease in weight from 68 to 60 Kg., was accompanied by retention of a large amount of nitrogen.

HANSEN, Minneapolis.

QUANTITATIVE STUDIES ON THE REPLACEMENT OF BODY CHLORIDES. R. M. BARTLETT, D. L. C. BINGHAM, S. PEDERSEN, W. G. MADDOCK and F. A. COLLER, Proc. Soc. Exper. Biol. & Med. **38**:89 (Feb.) 1938.

The theoretic amount of sodium chloride needed was based on the consideration that the average chlorine content of the human body is 0.15 per cent of the total body weight; in terms of sodium chloride the amount is 0.248 per cent of the total body weight. Using 560 mg. per hundred cubic centimeters as the normal level of the chlorides in the plasma, the authors found the following formula for determining the optimal amount of sodium chloride to be retained to restore body chlorides to normal in patients with hypochloremia. The number of grams of sodium chloride needed equals the normal salt content of the body times the percentage of the depletion of plasma chlorides, which equals 0.248 per cent of the

$$\text{body weight (in Gm.)} \times \frac{560 - \text{level of depleted plasma chloride}}{560}.$$

On the basis of this formula it has been found that the administration of 0.5 Gm. of sodium chloride per kilogram of body weight for each 100 mg. per hundred cubic centimeters that the plasma chlorides need to be raised may be expected to restore the body chlorides to a normal level.

HANSEN, Minneapolis.

AN EXPERIMENT ON THE NUTRITIVE VALUE OF WINTER-PRODUCED "SUMMER" MILK. J. C. DRUMMOND, E. SINGER, S. J. WALSON, W. S. FERGUSON and M. S. BARTLETT, J. Hyg. **38**:25 (Jan.) 1938.

During the past twenty-five years it has been demonstrated that carotenoids of food influence the color of cow's milk—that carotene is transferred to the nutritive value of butter, that it can replace vitamin A in the diet (i. e., it is a precursor of that vitamin in the body) and that the diet of the cow determines the amount of vitamin A in the milk; also, that the vitamin A content may be different in milks from different breeds of cows although the rations may be the same. The level of vitamin A is highest in early summer, when the cows are on fresh pasture. It is lowest at the end of the winter. By replacing 70 per cent of the typical winter ration by artificially dried grass or lucerne the summer levels of carotene and vitamin A are maintained at from 0.8 to 0.5 mg. per hundred grams of fat. In the control groups the level of vitamin A dropped to about 0.2 mg. Because of the recognized importance of vitamin A in the nutrition of the growing child, 159 institutional children of the ages 5 to 16 were given the high carotene milk from October to March while those of a like control group were kept on the regular winter milk. The other foods given were identical in the two groups. Under medical supervision measurements of height, weight and chest were taken periodically, and no difference in the condition of health or growth could be detected between the two groups. It is believed that the basal diet of the two groups which was that usually given was already adequate in carotene and vitamin A.

JANNEY, Wauwatosa, Wis.

NUTRITION AND BASAL METABOLISM DURING GROWTH. P. NOBÉCOURT, Gaz. d. hôp. **111**:221 (Feb. 16) 1938.

This article is a classroom lecture based almost exclusively on data published by American authors: Aub and DuBois; Talbot and Benedict.

Nobécourt's conclusions are: The basal metabolism is an expression of the nutritive activities of the cells. Although the different authors give different values as standard, they all agree that the basal metabolism increases in relation to the surface area unit or the weight unit up to the end of the second year, then gradually decreases up to the twentieth year, then remains stable for two decades, after which another gradual decline is observed.

The basal metabolism of girls is lower than that of boys from the third year on. The basal metabolism is constant in relation to height between 80 and 120 cm. —i. e., between 2 and 8 years in boys and between 2 and 9 years in girls. Above this height the basal metabolism per centimeter of height is somewhat higher.

KAJDI, Baltimore.

IS THE ESTABLISHMENT OF A STATION FOR THE COLLECTION OF HUMAN MILK LIKE THE ONE IN ERFURT DESIRABLE? P. FELDWEG and M. KAYSER, München. med. Wchnschr. **84**:1708 (Oct. 22) 1937.

This article in answer to a criticism by Dr. J. Haarer describes the value of the "human milk station" established in Erfurt, Germany. The station was established ten years ago. Last year 6,000 liters of milk were collected. One of the chief objections was that such a milk station tends to increase the number of women who do not nurse their infants. This is denied by the authors. With proper technic 90 per cent of the mothers have sufficient breast milk and half of these have more than enough. The milk costs 4.50 marks per liter. Is it not better to pay that much for the human milk than to let the sick children drink cow's milk and die? Each death of an infant weakens the national strength.

BRAHDY, Mount Vernon, N. Y.

DISSOCIATION OF WATER AND SALT METABOLISM IN SOME KINDS OF MALNUTRITION IN INFANCY. E. HAINISS, Orvosi hetil. **81**:1285 (Dec. 18) 1937.

Hainiss proved through animal experiments that in some cases of malnutrition in infancy the organs, in spite of the fact that they are poor in salt, are rich in water. In these cases the salt and water metabolism dissociate. Parallel with the poverty in salt the protein content diminishes, and this low protein content diminishes the oncotic pressure, which in turn throws difficulties in the way of the water stream to the blood. Therefore the organs, in spite of their great loss of salt, remain relatively rich in water. The form of malnutrition which is characterized by hyposalemia, hypoproteinemia and relative richness in water is called by Hainiss a "decompositional form" of malnutrition.

GÖTTCHE, Budapest, Hungary.

Vitamins; Avitaminoses

OBSERVATIONS ON THE RENAL THRESHOLD FOR ASCORBIC ACID IN MAN. J. M. FAULKNER and F. H. L. TAYLOR, J. Clin. Investigation **17**:69 (Jan.) 1938.

Observations on the level in the serum of ascorbic acid and the rate of urinary excretion of this vitamin in man (apparently all adults; ages not given) indicate that there is a renal threshold for this substance—that the critical level approximates 1.4 mg. per hundred milliliters of serum when the value of blood ascorbic acid is maintained at or above this, it corresponds to the so-called saturation state, while values below this threshold level correspond to the unsaturated state.

GUEST, Cincinnati.

TREATMENT OF HUMAN PELLAGRA WITH NICOTINIC ACID. P. J. FOUTS, O. M. HELMER, S. LEPKOVSKY and T. H. JUKES, Proc. Soc. Exper. Biol. & Med. **37**:405 (Nov.) 1937.

Four patients with pellagra were given nicotinic acid. One was given 1 Gm. daily. Three were given 500 mg. daily. All showed distinct improvement in general condition and mental attitude within forty-eight hours after the institution of therapy. The improvement was as satisfactory as that following administration of liver filtrate except for an increase in the time required for complete disappearance of the dermatitis.

HANSEN, Minneapolis.

CRYSTALLINE VITAMIN B-6. J. C. KERESZTESY and J. R. STEVENS, Proc. Soc. Exper. Biol. & Med. **38**:64 (Feb.) 1938.

Vitamin B_6, designated as the "rat pellagra preventing" principle by György (*Nature, London* **13**:498, 1934), has been isolated in crystalline form. The hydrochloride is freely soluble in water and sparingly soluble in alcohol and acetone. It is obtained as white platelets melting at 204 to 206 C., with decomposition. Assays in rats indicate the single curative dose of the crystalline preparation to be no more than 0.1 mg.

HANSEN, Minneapolis.

VITAMIN C CONTENT OF HUMAN NON-SCORBUTIC CEREBROSPINAL FLUIDS. W. W. JETTER and T. S. BUMBALO, Proc. Soc. Exper. Biol. & Med. **38**:164 (Feb.) 1938.

Fifty ambulatory patients were studied for vitamin C content of the cerebrospinal fluid; 33 were syphilitic, while the other 17 showed various types of disease. The diets of all were adequate according to usual standards. The ascorbic acid content of the serum varied from 0.7 to 2.1 mg., with a median of 1.2 mg., per hundred cubic centimeters. No correlation existed between the state of nutrition and the level of ascorbic acid. The majority of the subjects were between 25 and 65 years of age. The authors believe that the determination of the vitamin C content of the cerebrospinal fluid may become an aid in the diagnosis of avitaminotic states.

HANSEN, Minneapolis.

COMPARISON OF VITAMIN B_1 CONTENT OF RAW AND EVAPORATED MILK BY THE TEN-DAY BIO-ASSAY METHOD. A. L. DANIELS, Proc. Soc. Exper. Biol. & Med. **38**:212 (March) 1938.

Bioassay for the vitamin B_1 of commercial evaporated milk as compared with that of raw milk showed that twice as much of the evaporated milk was necessary to effect a certain gain in weight of test animals on B_1-deficient diets as of raw milk from Guernsey cows. Evaporation of the milk seemed to cause a 60 per cent loss in the amount of vitamin B_1.

HANSEN, Minneapolis.

EFFECT OF AUTOCLAVING ON VITAMIN POTENCY OF NICOTINIC ACID. S. G. SMITH, G. MARGOLIS and L. H. MARGOLIS, Proc. Soc. Exper. Biol. & Med. **38**:251 (March) 1938.

Ten dogs were allowed to acquire blacktongue on a modification of Goldberger's diet. Half of the animals were given autoclaved nicotinic acid and the other half unautoclaved nicotinic acid. The symptoms cleared up equally rapidly in the two groups, and the symptoms recurred about the same time in each group when the nicotinic acid was discontinued. In this respect nicotinic acid resembles the PP factor of Goldberger.

HANSEN, Minneapolis.

INTRADERMAL TEST FOR VITAMIN C DEFICIENCY. B. PORTNOY and J. F. WILKINSON, Brit. M. J. **1**:328 (Feb. 12) 1938.

Although brief, this article does not lend itself to abstracting because of the technical descriptions. The summary is as follows:

A suggested intradermal test for subnutrition in vitamin C, in which use is made of 2,6-dichlorphenolindophenol, has been examined in a series of 103 patients. Prolongation of the decolorization appears to run parallel to the vitamin C content of the tissues, although other reducing substances in the skin may be concerned in the phenomenon of decolorization.

The method may be of value as a rapid clinical test for deficiency of vitamin C. A decolorization time of less than five minutes indicates saturation of the tissues with vitamin C, while one of ten minutes or longer is in favor of a diagnosis of deficiency.

ROYSTER, Charlottesville, Va.

A Possible Discrepancy in the Estimation of Ascorbic Acid in Urine. G. W. T. H. Fleming and T. E. Burrows, Brit. M. J. **1**:333 (Feb. 12) 1938.

This study in laboratory technic does not lend itself to abstracting. The summary is as follows: Sulfuric acid, which was still being used to "preserve" ascorbic acid in twenty-four hour specimens of urine at the time of writing, has been shown to destroy ascorbic acid even when used in a concentration of 1 per cent; with stronger solutions the destructive effect is still greater.

Royster, Charlottesville, Va.

Severe Rickets with Multiple Spontaneous Fractures. R. Bevan, Proc. Roy. Soc. Med. **31**:361 (Feb.) 1938.

A girl 2 years of age, the last of 5 children, was fed breast milk and diluted cow's milk with orange juice but no cod liver oil. When she reached the age of 1 year, a mixed diet of mashed potatoes, apples and bananas was instituted, and occasionally minced meat or rabbit was added to it. Physical examination on admission to the hospital revealed an ill child, pale, with 60 respirations per minute and a grossly deformed chest. Signs of bronchitis were present in the chest. The forearms, arms and thighs were deformed. Roentgenograms of the bones showed acute epiphysial rickets, marked general decalcification of the bones, multiple greenstick fractures of the humeri, radiuses, ulnas and femurs and old fractures of the clavicles. Roentgen study of the lungs showed some opacity at the hilus of the left lung and the base of the right lung. The serum calcium was 4.93 mg. per hundred cubic centimeters of serum, and the phosphorus was 3.12 mg. per hundred cubic centimeter of serum. On treatment the child improved quickly. The notes on progress, the results of other investigations and the roentgenograms of the long bones are given in the report.

Williamson, New Orleans.

C Hypovitaminosis. L. Armentano and F. Novaszel, Orvosi hetil. **81**:869 (Aug. 21) 1937.

The best method for demonstrating C hypovitaminosis is the "saturation method": One should give a large amount of vitamin C intravenously (from 200 to 300 mg.) every day, and one should notice in how many days that amount of vitamin C leaves the organism. A healthy organism secretes 50 per cent of administered vitamin C either immediately or within from two to three days. In a person with hypovitaminosis this secretion begins only after the depots which are poor in vitamin C (adrenal cortex, pituitary body, liver) are filled. In such a person the secretion begins only in from seven to nine days and attains its greatest degree in from thirteen to sixteen days. Using this method, the authors found that acute infectious diseases always cause C hypovitaminosis, whereas they could not show regularly hypovitaminosis in other diseases except in protracted monotonous nutrition (ulcus diet). Hypovitaminosis may occur without any decided clinical signs. In patients with a hemorrhagic diathesis C hypovitaminosis does not play any role and treatment with vitamin C is absolutely useless.

Göttche, Budapest, Hungary.

Roentgenographic Study of Beriberi Heart. I. Kobayashi, Acta pædiat. japon. **43**:1786 (Dec.) 1937; **44**:23 (Jan.); 179 (Feb.) 1938.

Kobayashi presents comprehensive and accurate measurements, by the use of a planimeter on roentgenograms, of 200 beriberi hearts together with 36 normal hearts as controls. In the estimation of cardiac changes he emphasizes the importance of the lung-heart quotient (Groedel). The normal quotient is placed at 1.71 and with the exception of the cerebral type (1.82) the ratio in beriberi is usually low (from 1.19 to 1.43), indicating the relative enlargement of the heart.

This ratio is also helpful in differentiating the cardiac changes seen in nutritional disturbances in infants. In the beriberi type of such conditions the ratio is usually low, while in the nonberiberi type it is high, a point which may be used in the diagnosis of types of nutritional deficiency.

KATO, Chicago.

GLUTATHIONE IN INFANTILE BERIBERI. Y. KITAMURA, Acta pædiat. japon. **44**:274 (Feb.) 1938.

Using Tunnicliffe's method, Kitamura made quantitative determinations of glutathione in the blood of infants suffering from beriberi. In 16 normal infants the glutathione content of the blood varied from 19.7 to 31.3 mg. per hundred cubic centimeters, with an average of 24.7 mg. In 26 infants with beriberi the amount ranged between 15.4 and 29.5 mg., with an average of 22.7 mg. After treatment with preparations of vitamin B the glutathione content showed definite increase.

KATO, Chicago.

VITAMIN C CONTENT OF THE BRAIN OF THE NEWLY BORN RABBIT. H. FUJII, Acta pædiat. japon. **44**:291 (Feb.) 1938.

In the cerebrum, cerebellum and medulla of the newly born rabbit the quantity of vitamin C increases after birth and reaches its highest value on the third day; thereafter it declines gradually to reach the normal level. The colorimetric method with 2,6 dichlorophenolindophenol was used.

KATO, Chicago.

INHIBITION OF AUTO-OXIDATION OF VITAMIN C BY MEANS OF RABBIT LENS. H. FUJII, Acta pædiat. japon. **44**:613 (April) 1938.

Auto-oxidation of vitamin C in sterilized cow's milk, human milk and colostrum can be definitely inhibited by placing a rabbit's lens in each mlk.

KATO, Chicago.

SIGNIFICANCE OF VITAMIN C IN THE PRODUCTION OF EDEMA. J. DOI, J. Orient. Med. **28**:209 (Feb.) 1938.

I. *The Value of the Plasma Protein in Guinea Pigs Fed on a Vitamin C–Deficient Diet.*—Doi made determinations of the plasma protein in guinea pigs during a course of experimental scurvy and reports the following results: 1. During the first seven days of observation the albumin fraction showed a definite decrease, which was compensated by a tendency toward a slight increase in the globulin fraction, so that the total protein approximated the normal level. 2. During the second period of observation (from the eighth to the fourteenth day) a decrease was observed in total protein, brought about by a marked reduction in the albumin fraction. 3. In the third period (from the fifteenth to the twenty-first day) all fractions of plasma protein were decreased, the reduction being most marked in albumin. 4. It was further observed that the reduction in plasma protein was closely associated with increased capillary permeability as the basis of edema. Thus vitamin C appeared to have an important relation to the occurrence of edema.

II. *Changes in the Organs and in the Plasma Protein of Experimental Scorbutic Guinea Pigs.*—Doi made chemical analyses of the organs and plasma protein of experimental scrobutic guinea pigs and found that (1) the water content of the organs was increased, the muscles showing as much as three times the normal; (2) the total protein content of the liver, kidneys and lungs was diminished, that of the muscles remaining normal; (3) no significant changes occurred in the amounts of ashes from these organisms, and (4) all fractions of plasma protein decreased, the decrease being most marked in the albumin fraction. From these

observations Doi considers that the deficiency in vitamin C caused the reduction of osmotic pressure in the capillaries, due to loss of plasma proteins, which in turn caused the escape of water into the tissues through the capillary wall. This is considered added evidence in favor of a definite relation of C avitaminosis to the production of edema.

KATO, Chicago.

Hygiene; Growth and Nutrition; Public Health

RECENT DEVELOPMENTS IN THE MATERNAL AND CHILD-HEALTH AND CRIPPLED CHILDREN'S PROGRAMS IN THE SOUTHERN STATES. F. C. ROTHERT, South. M. J. **31**:692 (June) 1938.

Both in the maternal and child health program and in the crippled children's program the Southern states provide an interesting diversity of local problems. There are even more striking differences in the approach to similar general problems and in the selection of problems for attack. The two programs provide interesting contrasts, for in one the element of education and in the other the element of medical care has been most emphasized.

In each program things are learned which can be applied to the other.

SCHLUTZ, Chicago.

HEALTH OF THE SCHOOL CHILD. Brit. M. J. **1**:35 (Jan. 1) 1938.

This is a brief summary of a health officer's report. It cannot really be abstracted. The author enters into such studies as nutrition of the school child, provision of free meals and milk, physical education, medical inspection and medical treatment.

ROYSTER, Charlottesville, Va.

OBSERVATIONS ON THE HEIGHTS AND WEIGHTS AND GROWTH OF PRE-SCHOOL CHILDREN IN THE CITY OF MELBOURNE. H. E. KINCAID and M. STUCKEY, M. J. Australia **1**:575 (March 26) 1938.

Kincaid and Stuckey present graphs, and an analysis of the graphs, compiled from 10,000 records of the height and weight of 2,800 children between the ages of 2 and 6 years, showing: (1) the average height and weight for age of all children observed; (2) the curve of height for age for children without defects, which is seen to be slightly above the average curve; (3) the curve of weight for height for children without defects, which likewise is found to be well above the average curve for the whole group, the difference becoming greater as the height increases; (4) a comparison with figures given by Emerson; (5) a regular advance in height throughout the year but a rapid increase in weight during summer and autumn and practically stationary weight during the latter part of the winter and the whole of spring.

GONCE, Madison, Wis.

Prematurity and Congenital Deformities

CONGENITAL TRANSPOSITION OF THE GREAT ARTERIAL TRUNKS. D. W. INGHAM and F. A. WILLIUS, Am. Heart J. **15**:482 (April) 1938.

Five cases of transposition of the great arterial trunks are reported. In 1 instance partial transposition was present, both the aorta and the pulmonary aorta arising from the right ventricle. In the 4 other cases complete transposition was present.

In 4 cases the ductus arteriosus was patent, and in 4 instances the foramen ovale was patent. An interventricular septal defect occurred in 2 cases. In 2 instances situs in versus was an associated condition. A systolic murmur was heard in 4 of the 5 cases. The age at death varied from 18 days to 7 months.

GIBSON, Chicago.

FAMILIAL CLUBBING OF THE FINGERS AND TOES. D. R. SEATON, Brit. M. J. **1:** 614 (March 19) 1938.

Seaton reports on three generations with clubbing of fingers and toes, apparently of congenital origin. According to this case report, the anomaly is apparently along dominant mendelian lines.

ROYSTER, Charlottesville, Va.

MORTALITY AMONG PREMATURE INFANTS. H. SIEDENTOPF, München. med. Wchnschr. **84**:884 (June 4) 1937.

The great importance of the birth rate for the future of the German people is generally recognized. About 10 per cent of all births are premature. During the years from 1920 to 1923 there were 1,012 premature infants delivered in one hospital in Leipzig. There were 707 liveborn, but 152 of these died in the hospital. Since these premature infants left the hospital (from ten to fourteen years ago) an additional 179 have died. None of the 32 liveborn babies weighing under 1,000 Gm. left the hospital alive. There were 75 liveborn infants weighing between 1,000 and 1,500 Gm., of whom 49 died in the hospital and 15 after discharge. No data could be obtained about the remaining 11. Of the total 707 live premature infants, 188 are known to be alive after ten years and another 188 could not be traced.

Premature infants are especially susceptible to infectious diseases, gastrointestinal disturbances and the development of rickets, and a great many die as a result of these diseases. To prevent this, Siedentopf advises prolonged institutional care.

BRAHDY, Mount Vernon, N. Y.

INTRAUTERINE ACQUIRED (NOT INHERITED) MALFORMATIONS. B. SZENDI, Orvosi hetil. **81**:1034 (Oct. 9) 1937.

Two couples of monozygotes were observed. One of each couple showed great malformations; the other was totally healthy. In the case of the first couple, beside the healthy fetus, the other was born with spina bifida and a tumor in the mouth. In the case of the second couple, beside the healthy fetus, the other showed spina bifida and hydrocephalus (1,250 cc. of cerebrospinal fluid). In both cases a great hydramnion could be observed. Since both couples were monozygotes, it is obvious that the malformations were not inherited but acquired during intrauterine life.

GÖTTCHE, Budapest, Hungary.

Acute Contagious Diseases

CHEMOPROPHYLAXIS IN POLIOMYELITIS: THE TECHNIC OF APPLYING CHEMICAL AGENTS TO THE OLFACTORY MUCOSA. L. SHAHINIAN, J. A. BACHER, R. C. MCNAUGHT and R. R. NEWELL, J. A. M. A. **110**:1254 (April 16) 1938.

This article describes the technic found to be most effective for intranasal administration of chemicals for the prevention of poliomyelitis. The head should not be held in the Praetz position but inverted completely, so that the base line of the skull is horizontal. By clinical and roentgenologic studies a dose of 0.5 cc. was found necessary to cover the olfactory membrane in the superior meatus in every child.

HEERSMA, Kalamazoo, Mich.

OPSONOCYTOPHAGIC TEST IN CHILDREN WITH PERTUSSIS AND IN CHILDREN VACCINATED WITH H. PERTUSSIS ANTIGENS. C. SINGER-BROOKS and J. J. MILLER JR., J. Clin. Investigation **16**:749 (Sept.) 1937.

The recent adaptation of the opsonocytophagic test to the study of pertussis has been scrutinized. A high opsonocytophagic titer of the serum was found for children during and after attacks of pertussis and after injection of Haemophilus

pertussis vaccine. Control studies of normal infants and children were made simultaneously. The authors conclude that the test may be of value in estimating the potency of H. pertussis antigens but that it is not adequate as a test of immunity.

GUEST, Cincinnati.

EFFECT OF IMMUNE BLOOD ON THE OPSONO-CYTOPHAGIC POWER OF THE BLOOD IN PERTUSSIS. W. L. BRADFORD, R. MIKELL and B. SLAVIN, J. Clin. Investigation **16**:829 (Sept.) 1937.

In groups of infants (from 3 to 13 in each group) increases in the opsonocyptophagic power of the blood were found after injections of adult immune blood serum, intravenous blood transfusions and injections of intramuscular placental extract.

GUEST, Cincinnati.

ANALYSIS OF THE 1935 EPIDEMIC OF INFANTILE PARALYSIS IN MASSACHUSETTS. A. T. LEGG, New England J. Med. **217**:507 (Sept. 23) 1937.

In 1935 Massachusetts suffered an epidemic of infantile paralysis similar to those of 1916, 1927 and 1931. The incidence of cases in these years was 1,927 in 1916, 1,189 in 1927, 1,429 in 1931 and 1,392 in 1935.

Of the cases occurring in 1935, the Harvard Commission Clinic at the Children's Hospital saw 28.4 per cent (397 cases) by Jan. 1, 1936, and 33.1 per cent (462 cases) by May 22, 1936. There were 5 cases that occurred out of the state.

The eastern part of the state was the most severely affected, with Boston and vicinity reporting 545 cases. The rate of occurrence in Boston was 0.55 per thousand.

As in former years, the greatest number of cases occurred in the late summer and early fall, with 482 cases in August and 537 in September, the incidence dropping to 235 in October and to 58 in November.

The average age of the patients encountered by the Commission was 6.9 years for the males and 7.3 years for the females.

In each of two families 3 cases were found and in each of three families 5 cases.

The average time at which the cases were seen after onset was thirty-two days.

At their first examination 9.5 per cent of the patients were normal, 39.2 per cent had paralysis of the arms, 79.9 per cent had paralysis of the legs and 72.4 per cent had paralysis of the trunk.

The average severity of the paralysis of patients with involvement of their arms was 13.3 per cent; of those with involvement of their legs 17.8 per cent, and of those with involvement of their trunks 17.2 per cent.

The severity of the paralysis appeared to have no relation to the age. In frequency and severity of involvement this epidemic corresponded in the main with that of 1927. The severity and extent of the paralysis in 1935 when compared with that of other years were less.

GENGENBACH, Denver.

A NEW TECHNIC FOR VACCINATION AGAINST SMALLPOX. H. J. FREEDMAN, New England J. Med. **217**:953 (Dec. 9) 1937.

Freedman uses a punchlike scarifier, made of stainless steel and having on one end two concentric edges in the same horizontal plane, the diameter of the outer edge being 2.3 mm. The skin is washed with soap and water and permitted to dry before the drop of vaccine is applied. The penetration is made with one complete turn of the scarifier through the vaccine into the skin. The typical vaccinal lesion appears in from two to seven days, and the terminal scar measures from 0.3 to 1 cm. in diameter. In 150 children between 6 months and 5 years of age there were 93 per cent takes. Of the 11 children whose vaccination failed to take, 5 were revaccinated two or more times without result.

GENGENBACH, Denver.

ACCIDENTAL SMALLPOX VACCINATION AND ECZEMA VACCINATUM. G. W. GRAVES and C. DOWMAN, New York State J. Med. **37**:1833 (Nov. 1) 1937.

Two fatal cases are reported. One occurred in a Negro boy of 2½ years who had had eczema for one and a half years. The infection was traced to a sister who had recently been successfully vaccinated.

The second case was that of a white boy 1 year of age who had had eczema for three months. Eighteen days prior to admission a 2 year old brother had been vaccinated. The brother's vaccination had been protected by a dressing and had never been scratched or broken. Thirteen days later the patient's face and left eyelid became swollen, and three days later lesions appeared on the abdomen, wrists, thighs and knees. The child died on the nineteenth day of the disease.

Eczema vaccinatum and generalized vaccinia are essentially the same, and in both conditions the virus is probably disseminated by the blood, the lesions developing in the eczematous areas, where resistance has been lowered.

Vaccinations should be avoided or else carefully managed in families in which eczema exists.

AIKMAN, Rochester, N. Y.

DIPHTHERIA OF THE SKIN. I. PINCUS, New York State J. Med. **37**:1938 (Nov. 15) 1937.

The case is one of the "false membrane, paronychia-like type described in European literature." The child first had a bloody nasal discharge and cervical adenitis. An incision was made for drainage, and a culture of the hemolytic streptococcus was obtained. Infections occurred at the bases of the nails, and later urticaria developed. It was not until the eighth week that cultures positive for diphtheria were obtained from the fingers and nose. Prompt recovery occurred after treatment with diphtheria antitoxin. The pediatric ward was found to have 4 diphtheria carriers.

AIKMAN, Rochester, N. Y.

ISOLATION OF POLIOMYELITIC VIRUS FROM HUMAN STOOLS. J. D. TRASK, A. J. VIGNEC and J. R. PAUL, Proc. Soc. Exper. Biol. & Med. **38**:147 (Feb.) 1938.

A virus fulfilling the clinical and pathologic criteria for identification as the virus of poliomyelitis was recovered from the stools of a child with abortive poliomyelitis on the second, fourteenth and twenty-fifth days after onset. Stool specimens on the forty-third and sixty-fourth days failed to yield the virus. By intracerebral and intra-abdominal injection of this virus into a monkey twice and intra-abdominal inoculation alone once, the authors succeeded in identifying the virus.

HANSEN, Minneapolis.

CHEMOTHERAPY OF B PERTUSSIS INFECTIONS OF MICE. P. GROSS, F. B. COOPER and M. LEWIS, Proc. Soc. Exper. Biol. & Med. **38**:407 (April) 1938.

Sulfanilamide had no therapeutic value in the treatment of mice infected intra-abdominally with a virulent culture of Bacillus pertussis.

HANSEN, Minneapolis.

PREVALENCE OF COMMUNICABLE DISEASES IN THE UNITED STATES. Pub. Health Rep. **53**:551 (April 15) 1938.

In the period from Feb. 27 to March 26, 1938, measles continued to increase, 172,626 cases being reported, which is three times the median for this period. There were 2,056 cases of smallpox, two and a half times the average, and a slight increase in typhoid. This was due to the large number of cases in Louisiana (98). Meningitis, diphtheria, influenza and scarlet fever were below the average. The average mortality from all causes was 12.2 per thousand. This is below the average.

SANFORD, Chicago.

SERUM AND OTHER SPECIFIC TREATMENTS OF SMALLPOX. P. T. PATEL, J. Indian M. A. **7**:847 (March) 1938.

Patel reports that the use of convalescent serum and of serum from immunized animals was ineffective in controlling and modifying the various stages of smallpox and in influencing the mortality of the disease. GONCE, Madison, Wis.

REPORT OF THE QUEENSLAND ROYAL COMMISSION ON MODERN METHODS FOR THE TREATMENT OF INFANTILE PARALYSIS. M. J. Australia **1**:187 (Jan. 29) 1938.

The assignments of the royal commission appointed in Brisbane, Queensland, by the state government in October 1935 were to investigate in general modern methods of treatment of infantile paralysis and other diseases of a paralytic nature, to investigate in particular the Elizabeth Kenny method of treating infantile paralysis, spastic paralysis and birth palsy and to compare the results of this method with the results of orthodox treatment. The first part is devoted to an extensive review of the anatomy, physiology, epidemiology, pathology, clinical picture and orthodox treatment of infantile paralysis. This is followed by a report on the chief assignment of the investigation, namely, a comparative study of the Kenny and orthodox methods of treatment of paralyses.

Miss Kenny lays down five principles of treatment: (1) maintenance of a bright mental outlook, (2) maintenance of impulse, (3) hydrotherapy and remedial work, (4) maintenance of circulation, (5) avoidance of the generally accepted methods of immobilization. With regard to 1, Miss Kenny is to be commended for stressing a principle which is practiced in the therapeutic departments of all hospitals. By "maintenance of impulse" Miss Kenny apparently means maintenance of the nervous impulse to the muscles from the brain centers. In reeducating affected muscles Miss Kenny asks patients to visualize the part to be moved. This, of course, has its limitations, for very young patients, the majority, are incapable of visualizing. In the use of hydrotherapy the commission concurs but only within reasonable limits. Miss Kenny lays great stress on the importance of the individual bath, but the commission feels that as routine practice this is entirely unnecessary in many cases and would be too expensive.

The maintenance of good circulation, stressed by Miss Kenny, is recognized as essential in orthodox treatment. However, she considers that immobilization reduces the vitality of the circulation to such an extent that it should be abandoned. The commission does not agree that in properly applied appliances the circulation is impaired.

The fifth principle, the abandonment of immobilization, is revolutionary and in the opinion of the commission a retrograde step. Even though deformities due to contracture may be prevented in some instances by daily movements of the joints it is not possible to prevent the development of severe deformities in spinal and abdominal pareses when splinting is abandoned. It is quite certain, too, that the Kenny method of treatment, which avoids splinting and so allows stretching of muscles, would encourage the development of much more deformity than the orthodox method in patients who have to leave the clinic uncured. It would be particularly damaging to adopt this nonsplinting and daily joint-moving method as is done in the Kenny method of treating poliomyelitis in the acute and early stages, owing to the failure of the method to prevent injury due to stretching of muscles and deformity due to muscular imbalance.

The exercises described for muscle training are practically the same as those that have been used in orthodox practice for many years. The hot and cold sprays recommended by Miss Kenny to improve the circulation in affected limbs have no advantages over radiant heat, diathermy and massage. The commission finds that certain of Miss Kenny's apparatus are ingenious and useful. Her pulleys for treatment of spinal curvature and extensor paresis and her apparatus for measuring power of thrust in lower limbs should find a field of usefulness in orthodox practice.

The commission feels that Miss Kenny is to be commended for espousing the cause of children having spastic paralysis. Her methods differ in no way from those of orthodox practitioners, but she has thought out some ideas that are new at least to reeducators in Queensland, viz., the coir matting, the sand pit and walking up stairs. However, the commission believes that orthodox treatment given the facilities, the time and the financial aid could and would produce similar results. Clinically, birth palsy is strictly comparable with poliomyelitis, and all references to the reeducative treatment of patients suffering from the latter disease apply exactly to the treatment of patients presenting birth palsy, with even more stress on the necessity of proper splinting.

The commission cannot recommend the application of the Kenny method to the treatment of cripples at any stage of paralysis, and especially not to the treatment of those whose disabilities are in the acute or early stage. Miss Kenny, liberally supplied with funds, has achieved a certain amount of success, but this is due to the intensity rather than to the nature of the treatment. Given the same intensity of application, orthodox methods would produce better results.

GONCE, Madison, Wis.

SOME LABORATORY EXPERIMENTS WITH A SYDNEY STRAIN OF POLIOMYELITIS VIRUS. W. C. SAWERS, M. J. Australia **1**:305 (Feb. 12) 1938.

A 10 per cent suspension of the dorsal spinal cord of a child who died of acute poliomyelitis in Sydney, Australia, was used in amounts of 0.5 cc. intracerebrally and 2 cc. intraperitoneally to produce paralysis in monkeys of the species Macacus rhesus. There was no effect on calves and sheep when a suspension of the virus was injected into these animals. Neutralization tests and protective tests with various immune serums showed high neutralization by immunized sheep serum from the United States when this serum was tested against virus obtained from the Sydney child. Sawers feels that this indicates a similarity between the United States and the Sydney strains of poliomyelitis virus.

GONCE, Madison, Wis.

A NEW SPIROCHETOSIS. E. LESNÉ, J. TROISIER and H. BÉNARD, Rev. franç. de pédiat. **13**:507, 1937.

A girl 13 years old was brought to the hospital because of fever, vomiting, constipation and diffuse abdominal pain. Because the last was most pronounced in the right iliac fossa, an appendectomy was performed. The appendix, however, was normal. Headache and fever continued, and an enlargement of the spleen was made out by percussion, although it could not be palpated. All other examinations and ordinary laboratory procedures yielded no information. A blood culture in broth showed on the fifth day spiral organisms measuring from 2 to 30 microns in length and showing from two to ten turns. A second blood culture, a week later, was negative, and the child made an uneventful recovery, the fever falling by lysis. Injection of the infected broth into a monkey and into 2 patients with dementia paralytica resulted in a rise of temperature with malaise on the fifth day. The spirochete corresponded morphologically to one described by Pons in 1923, and the clinical course of the disease was similar to that described by him.

LESLIE, Evanston, Ill.

VACCINATION AGAINST WHOOPING COUGH. R. AGRELO, Rev. méd. latino-am. **23**: 580 (Feb.) 1938.

This is a survey of medical opinions gathered from physicians in France, Switzerland and the Argentine Republic on the value of whooping cough vaccine. Of 51 clinicians questioned, 35 gave unfavorable opinions on the prophylactic value of vaccination. As to the treatment of whooping cough with vaccine, 18 gave favorable opinions, while 13 said the effects were doubtful and irregular.

DWYER, Kansas City, Mo.

POLIOMYELITIS IN SCHWÄB.-HALL IN 1935. M. KIBLER, München. med. Wchnschr. **84**:91 (Jan. 15) 1937.

Kibler reports his observations during an epidemic of poliomyelitis in 1935. The first patient died of ascending paralysis. During the next two weeks only 2 patients were admitted to the hospital, but in the following three weeks 58 were admitted. The total number observed was 86. None of the symptoms were diagnostic, and Kibler depended on changes in the spinal fluid to establish the diagnosis. All patients received convalescent serum intramuscularly as soon as the diagnosis was made. The lumbar puncture seemed to relieve the restlessness and pain in many cases. The injection of serum was harmless and in many instances seemed to result in improvement. However, since the disease is frequently mild, it is difficult to separate cures post hoc from those propter hoc.

The author found that apparently well children who were in contact with patients before they were hospitalized had asymptomatic poliomyelitis. He gives two illustrations. Four sisters of one patient were apparently well, but all had abnormal cerebrospinal fluids under increased pressure. They received convalescent serum and made an uneventful recovery.

The disease is spread by patients during the period of incubation and by well persons with or without changes in their spinal fluid. In the latter instances transmission is probably by way of the hands or clothing. Strict isolation of patients for fourteen days is important in controlling an epidemic. Schools and churches should be closed and large gatherings forbidden.

BRAHDY, Mount Vernon, N. Y.

VACCINATION THROUGH THE NOSE. D. GYÜRE, Orvosi hetil. **81**:991 (Sept. 25) 1937.

The lymph was diluted with sodium chloride 1:4 and was pressed into the nose with a cotton tampon for five minutes. Gyüre found that immunizing power can be attained by this method without hurting the mucous membrane of the nose. The general symptoms are not more severe than with the common scratching method. The mucous membrane of the nose usually does not show any alterations; one can observe in some cases more or less hyperemia, in some cases a little secretion and in a few cases a small membrane. The changes in the mucous membrane disappear in one week.

GÖTTCHE, Budapest, Hungary.

CLINICAL STUDY OF GANGRENOUS DIPHTHERIA. T. CHO, Acta pædiat. japon. **43**: 1766 (Dec.) 1937.

In the University Clinic in Tokio a total of 32 patients with gangrenous diphtheria were seen in four years (1932-1936). They represented 5.3 per cent of all patients with diphtheria (608). This type of diphtheria occurred most frequently in children of 5 and 6 years of age and was very rare in infants. The gangrenous lesions were located in the tonsils, uvula, posterior part of the pharynx and in the hard and soft palate. Marked submandibular lymphadenopathy with edema was noted in 23 of the patients. Vomiting of coffee-colored material and of blood occurred in a few cases. Abdominal pain and a hemorrhagic tendency were frequent. Bradycardia (from 23 to 60 beats per minute) and hypotension (below 70) were serious manifestations. The mortality was 84.4 per cent.

KATO, Chicago.

A CASE OF DIPHTHERITIC BACTEREMIA. M. OHTA, Acta pædiat. japon. **44**:108 (Jan.) 1938.

A boy 8 years old was subjected to tonsillectomy and one week later was admitted to the Dairen Hospital with the complaint of sudden fever but no other constitutional symptoms. Before death a blood culture was positive for diphtheria, and at postmortem examination a pure culture of diphtheria organisms was

obtained from practically every organ. The author stresses the importance of the blood culture in cases of diphtheria of the malignant and hemorrhagic type.

KATO, Chicago.

Acute Infectious Diseases

IMMUNIZATION AGAINST RHEUMATIC FEVER WITH HEMOLYTIC STREPTOCOCCUS FILTRATE. V. P. WASSON, Am. Heart J. **15**:257 (March) 1938.

An attempt was made to immunize 34 children who had had one or more attacks of rheumatic fever with a stock filtrate of Streptococcus haemolyticus. A control series of children was observed simultaneously.

The treated children seemed to fare much better than the controls, as indicated by lessened incidence and severity of rheumatic phenomena and a more satisfactory state of the general health. Wasson feels, however, that the group of cases is too small to justify definite conclusions.

GIBSON, Chicago.

THE SOURCE OF INFECTION IN PUERPERAL SEPSIS. B. DURIE, M. J. Australia **1**:242 (Feb. 5) 1938.

Durie stresses the danger of the carrier of a hemolytic streptococcus of Group A as a source of puerperal sepsis. Methods of isolating this group from the nonpathogenic groups are discussed. The various strains are isolated by the use of Griffith's type series and the precipitin test described by Lancefield. The importance of the hemolytic streptococcus as a source of danger to the newborn by invasion through the upper part of the respiratory tract and through the skin is stressed.

GONCE, Madison, Wis.

A NOTE ON THE SOCIAL ASPECTS OF RHEUMATISM. F. J. POYNTON, M. J. Australia **1**:555 (March 26) 1938.

In a short article Poynton discusses the influence of climate and surroundings on the incidence of rheumatism. Two aspects of climate are considered: the macroclimate, or general climate, and the microclimate, i. e., the conditions and environments of dwellings. The influence of heredity, of poverty and of the adaptability of the human being are also discussed briefly.

GONCE, Madison, Wis.

PROPHYLAXIS OF GAS GANGRENE IN MAN. W. J. PENFOLD and J. C. TOLHURST, M. J. Australia **1**:604 (April 2) 1938.

The authors report the production of antitoxin in man following the injection of alum-precipitated Bacillus welchii toxoid (the details of preparation of which are given). The authors so far are uncertain as to the proper dosage, the proper intervals between doses and the duration of the immunity.

GONCE, Madison, Wis.

ACUTE RHEUMATISM OCCURRING IN THE COURSE OF A STAPHYLOCOCCAL SEPTICAEMIA. F. D. HART, Proc. Roy. Soc. Med. **31**:357 (Feb.) 1938.

A boy of 7 years fell 40 feet (12 meters) out of a window and fractured the shaft and lower epiphysis of the right femur. His chin was cut, the mandible exposed and fractured and its periosteum torn. On his admission to a hospital the leg was submitted to extension, and the wound in the chin was cleaned and sutured. For the next few days there was an irregular temperature, but about the fifth day the temperature rose to 103 F., and a hectic fever continued for six days, when a parotid abscess was opened. The temperature fell but rose again in four days. The discharge showed pus cells and gram-positive cocci in chains but no growth. An abscess in the right inguinal region was opened, and the discharge showed a heavy growth of the hemolytic streptococcus. The fever con-

tinued, and roentgenograms taken two weeks later showed osteomyelitis of the femur, a dark shadow at the apex of the right lung and the heart enlarged. Twelve days later there were definite signs of pericardial effusion. A blood transfusion of 250 cc. was given. A swelling in the right supraclavicular region appeared. A blood culture at this time showed Staphylococcus aureus, and a nodule was found on the right elbow. The fever continued for another three months, but the child appeared surprisingly fit. The nodules around the elbow grew larger, and there was one noted on the left patella. These nodules were excised and on microscopic examination showed the changes typical of acute rheumatism. The child commenced to improve about this time and continued to do so.

WILLIAMSON, New Orleans.

THE SULFUR OF THE BLOOD IN CHILDHOOD: III. THE BLOOD SULFUR—NEUTRAL AND OXIDIZED—IN TYPHOID FEVER. I. BIDDAU, Riv. di clin. pediat. **36**:193 (March) 1938.

Sulfur was determined in the blood of 21 children during the different stages of typhoid fever. While the total nonprotein sulfur was not increased appreciably during the disease, the neutral sulfur fraction showed a distinct increase during the more active stages. Thus, the $\frac{\text{neutral S}}{\text{total S}}$ was 0.35 during the height of the disease, 0.24 during defervescence and 0.19 during convalescence. The normal ratio was 0.17.

HIGGINS, Boston.

POLYSEROSITIS. M. MANEKE, Monatschr. f. Kinderh. **73**:51 (April) 1938.

Maneke reports 4 cases of polyserositis and draws the conclusion that while this condition in adults may be on a tuberculous basis, in childhood it is usually a matter of purulent inflammation, often due to pneumococcic infection.

GERSTLEY, Chicago.

Chronic Infectious Diseases

THE URINARY OUTPUT OF VITAMIN C IN ACTIVE TUBERCULOSIS IN CHILDREN. W. W. JETTER and R. S. BUMBALO, Am. J. M. Sc. **195**:362 (March) 1938.

Jetter and Bumbalo show decreased urinary excretion of vitamin C in all 37 patients in the children's wards of the tuberculosis service of the Buffalo City Hospital on a daily ration of from 55 to 65 mg. daily. Their average was 5.7 mg. as compared with an average of 29.2 mg. for the 25 normal control children. The greater the severity of the tuberculous process, the lower the excretory figures.

The authors conclude that the usual type of diet is inadequate for tuberculous patients. A supplementary addition of the vitamin seems advisable.

HENSKE, Omaha.

DAILY VARIATIONS IN THE TUBERCULIN REACTION. J. S. HOWE, Am. Rev. Tuberc. **37**:264 (March) 1938.

A modification of von Gröer's method of making the tuberculin test daily was applied to 4 patients with pulmonary tuberculosis and 2 control subjects with positive reactions to tuberculin but no roentgen or clinical evidence of tuberculosis. The reactions in both the subjects and the controls showed marked daily fluctuations varying from 100 to 50 per cent of the maximal reactions to the doses used. The extent of the daily variation suggests the necessity of caution in drawing conclusions or in making clinical correlations from single tuberculin reactions at long intervals.

EUGENE H. SMITH, Ogden, Utah.

DAILY VARIATIONS IN THE TUBERCULIN REACTION: II. RELATION TO THE VASCULAR PRESSOR EPISODE. J. S. HOWE, Am. Rev. Tuberc. **37**:273 (March) 1938.

There is a definite correlation between quantitative variation in the tuberculin reaction and the state of the peripheral vessels as measured by daily determinations of diastolic blood pressure. Vasoconstriction, characterized by increased diastolic blood pressure, is accompanied by decreased or even negative reaction to tuberculin. The reverse is true of peripheral vasodilatation and is especially marked immediately following a decided pressor episode. Diastolic pressure was found to be definitely influenced by meteorologic environment, particularly by an infall of polar air, which causes peripheral vasoconstriction and is reflected as the "pressor episode." The mechanism of these variations in the tuberculin reaction appears to be one of periodic changes in vascular and tissue permeability, affecting the extent of local exudation in response to a definite dose of tuberculin.

EUGENE H. SMITH, Ogden, Utah.

PROGRESSIVE PRIMARY COMPLEX. O. AUERBACH, Am. Rev. Tuberc. **37**:346 (March) 1938.

While in the great majority of cases primary tuberculous infection goes on to anatomic healing, in a small number the disease becomes progressive. Primary foci in children under 1 year of age tend to liquefy, while those occurring in older children usually heal. Of 17 children with progressive primary disease, 15 were between 1 and 3 years of age. With one exception all were Negroes. The characteristic observation at autopsy was a large irregularly demarcated area of caseation with no definite capsule, surrounded by pneumonic tissue.. In the later stages the area of caseation may progress to involve the greater part of a lobe. Liquefaction with evacuation of the liquefied material results in an irregular, shaggy excavation. In every case in this series in which liquefaction did not occur, there was evidence of hematogenous tuberculosis in the form of miliary acinous and sublobular foci throughout the lung. Wherever primary cavitation was present, the lungs were studded chiefly with large foci in the form of sublobular and lobular areas of caseous pneumonia. The lymph nodes draining the foci were extensively enlarged and completely caseous and frequently had undergone central liquefaction. The later, however, is not necessarily concomitant with liquefaction in the primary focus. Generalization in the form of large nodular tuberculosis was present in all cases, and tuberculous meningitis caused the death of 9 patients. Extensive intestinal ulcerations were present in all patients with cavity formation.

EUGENE H. SMITH, Ogden, Utah.

THE TESTING OF ACTIVITY OF CHILDHOOD TUBERCULOSIS. W. A. MCGEE, J. A. M. A. **110**:718 (March 5) 1938.

The results of studies of the blood were compared with clinical and roentgen observations in 40 cases of childhood tuberculosis of various degrees of severity. Erythrocyte sedimentation tests and Schilling differential counts done by the same observer were found to be reliable prognostic aids. A high percentage of immature polymorphonuclear leukocytes was of ill omen. Lymphocyte-monocyte rations were less useful. The earliest pathologic changes were detected by the Schilling index.

HEERSMA, Kalamazoo, Mich.

TUBERCULOSIS OF THE SPINE IN CHILDREN. E. F. CAVE, New England J. Med. **217**:853 (Nov. 25) 1937.

This paper presents certain conceptions of tuberculosis of the spine in children. It is based on a study of 122 consecutive cases, covering a period of seventeen years.

The average age at the time of admission was 4.8 years. This average has been steadily diminishing during the past fifteen years. The average duration of the disease before admission was twenty months.

Tuberculosis of the spine is a blood-borne disease. It is metastatic, usually from the lungs, hilar nodes or cervical nodes. Rarely has the primary lesion been in the gastrointestinal tract.

The lesion of Pott's disease behaves differently in different sections of the spine. The cervical region was involved in 5 cases, or 4.1 per cent.

Pott's disease occurs most frequently in the dorsal portion of the spine; 96, or 78.7 per cent, of the children had thoracic lesions; in 6 these were cervicodorsal, in 64 dorsal and in 24 dorsolumbar. Involvement of the pedicles of the vertebrae is common in the dorsal region of the spine, and when this occurs deformity follows, usually to a marked degree.

Frequently in the acute stage of the disease lesions of the lumbar region of the spine are accompanied by spasm of the psoas muscles and abscesses of these muscles are common.

Signs of irritation or compression of the spinal cord occurring in Pott's disease are caused by constriction of the cord by tuberculous granulation tissue or by pressure from edema due to the disease process.

Cave believes that the patients do best without surgical intervention and should be treated through a well managed regimen including heliotherapy.

No operations are done during the acute stage of the disease or during the hot summer months.

The patients on whom spinal fusions were performed did well with the exception of the second patient operated on, who died from shock and exhaustion due to heat.

Among the 122 cases there was a mortality of 15.8 per cent; of the 19 deaths, 8 were due to amyloid disease. GENGENBACH, Denver.

TUBERCULOUS PERITONITIS IN CHILDREN. L. D. VAN ANTWERP, New England J. Med. **217**:995 (Dec. 16) 1937.

Of 3,125 patients admitted to a state sanatorium for tuberculous children, 41 had tuberculous peritonitis. Three of these left the institution within ten days, against advice. Of the remaining 38, 6 had serious complications, which resulted in a 100 per cent mortality of this group. Of the 32 patients without such complications, 9 died—a mortality of 28 per cent. In 4 patients under care for other tuberculous lesions peritoneal symptoms developed. The histories of these patients are presented in detail.

Treatment was in general supportive and palliative. Supportive treatment consists of such measures as rest in bed, the maintenance on a well balanced diet, exposure to sunlight and good nursing care. Palliative treatment consists mainly in aspiration of fluid when indicated for the patient's comfort and treatment for constipation or diarrhea as indicated. GENGENBACH, Denver.

MANTOUX TEST IN PEDIATRICS (INCREASED SIGNIFICANCE AND IMPORTANCE TO THE GENERAL PRACTITIONER—REPORT OF 1,000 CASES). J. BATTAGLIA, New York State J. Med. **37**:1901 (Nov. 15) 1937.

With the marked decrease in the incidence of positive skin tests for tuberculosis the Mantoux test becomes of more value in the diagnosis of tuberculosis. This test was made on 1,000 children in Kings County Hospital, Brooklyn, 0.1 mg. of old tuberculin being used, and 6.7 per cent positive reactions were obtained; 3.5 per cent of those tested had positive reactions without clinical evidence of tuberculosis; 3.2 per cent had positive signs. Of the positive reactors, 47.7 per cent gave clinical or roentgenographic evidence of tuberculosis. The Mantoux test should be performed on children as a routine.

AIKMAN, Rochester, N. Y.

TUBERCULOSIS IN INFANTS. D. PRICE, Brit. M. J. **1**:275 (Feb. 5) 1938.

This is a critical examination of a series of 78 cases of tuberculosis in infants who came under treatment during four years in St. Ultan's Hospital. Of these infants, 60 died and 18 recovered—giving a mortality of 77 per cent. The author feels that the contraction of disease in these cases was usually from the mother.

She also feels that abdominal tuberculosis is rare in the first year of life. She thinks that when it occurs it is apt to be due to ingestion of dried tubercle bacilli from floor dust as often as to ingestion of infected milk. The infant has little resistance to tuberculous infection. Inherited immunity may be regarded as negligible. The danger is in the development of acute miliary tuberculosis of the lung or meningitis from a primary (Ghon) focus. If a cavity is present, it is due to the breakdown of the primary focus or in other words to perifocal caseous pneumonia. In later childhood the adult type of phthisis may be seen.

The diagnosis depended on the tuberculin skin test; in infancy a positive reaction, she thinks, indicates an active lesion. Sixteen necropsies were performed, and the observations provided criteria for the interpretation of roentgenograms, which were universally resorted to. The history of contact in the home was definite in 70 per cent of the cases.

Her summary follows: 1. Seventy-eight cases of tuberculosis of the lungs are reported in infants under 1 year old: 23 per cent recovered.

2. Healing can be achieved only by early diagnosis—i. e., in the primary stage.

3. Early diagnosis can be made only by the tuberculin skin test, roentgenography and a history of contact.

4. Treatment consists mainly in immediate removal from contact with any one who has the disease and in rest.

ROYSTER, Charlottesville, Va.

ETIOLOGIC ROLE OF THE BOVINE TUBERCLE BACILLUS IN TUBERCULOUS MENINGITIS OF CHILDREN. E. LESNÉ and A. SAENZ, Rev. franç. de pédiat. **13**:457, 1937.

During the five years from 1932 to 1937 the authors studied 144 cases of tuberculous meningitis in children. From cultures made with the mediums of Löwenstein, 134 of the cases were found to be caused by the human bacillus and 9 by the bovine bacillus. The cultural differences of the two types of organisms are definite, and particulars are given. The incidence of bovine tuberculous meningitis in this series of cases was found to be much lower than that reported in England and Scotland. But even so the authors feel it accentuates the necessity for prophylactic measures in France. These consist in elimination of bovine tuberculosis, prohibition of the giving of raw milk to infants and strictly controlled pasteurization of milk.

LESLIE, Evanston, Ill.

TUBERCULOUS MENINGITIS IN INFANCY. B. SANCHEZ SANTIAGO and R. PEREIRAS, Arch. de med. inf. **7**:82 (March) 1938.

There is always some caseous ganglion giving rise to the disease. There is always some source of the contagion. The forms met with are somnolent, convulsive and classic (rare). The Mantoux test is positive except in much undernourished infants. The disease is always fatal.

SANFORD, Chicago.

SYPHILITIC MENINGITIS IN INFANCY. B. SANCHEZ SANTIAGO, Arch. de med. inf. **7**:172 (March) 1938.

Next to hydrocephalus, this is the commonest pathologic condition of the nervous system in infancy. It should be suspected in an infant with bulging of the fontanels and splenomegaly. The author's patients were treated with preparations of mercury, bismuth and arsenic.

SANFORD, Chicago.

SYPHILIS OF BONE IN A CHILD. H. G. HUBER, Monatschr. f. Kinderh. **72**:378 (March) 1938.

Huber reports, and illustrates by numerous roentgenograms, the case of a 13 month old infant in whom roentgen pictures of the bones showed typical scurvy. It was only after the child reached the age of 2½ years that the Wassermann reaction became positive and the roentgenograms typical of syphilis. At that time antisyphilitic treatment was instituted, with great improvement.

GERSTLEY, Chicago.

SIGNIFICANCE OF THE TRYPTOPHANE REACTION FOR THE DIAGNOSIS OF TUBERCULOUS MENINGITIS AND SATURNISM. Y. MIYAJIMA, Orient. J. Dis. Infants **22**:12 (July) 1937.

According to the observations of Kubota in the pediatric clinic at Kyoto Imperial University, tubercle bacilli can be demonstrated in the spinal fluid in 40 per cent of cases of tuberculous meningitis. In the cases in which the disease is in an early stage, however, the percentage of positive observations is much less than in those in which it is in a later stage. A positive tryptophan reaction, according to the reported observations of Burgi and others, occurs in practically all cases in which tuberculous meningitis is in an early stage. The author applied this method of study in 28 cases of meningeal manifestations in infants. The method consists in adding to from 2 to 3 cc. of spinal fluid 15 cc. of concentrated hydrochloric acid and 3 drops of 2 per cent formaldehyde; after five minutes the mixture is overlaid by 2 cc. of 0.06 per cent sodium nitroprusside. A violet ring appears at the point of contact of the overlaid solution in three minutes, indicating a positive reaction. In all of 10 cases of tuberculous meningitis the reaction was positive; of 9 cases of saturnism, the reaction was positive in 7 (valueless for differentiation), while in all of 4 cases of suppurative meningitis there were pseudo-positive reactions. Miyajima concludes that in the diagnosis of tuberculous meningitis in its early stage the tryptophan reaction is of definite value.

KATO, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

SEVERE FUNCTIONAL ANEMIA IN A CHILD, RESEMBLING PERNICIOUS ANEMIA OF ADULTS: A CASE STUDY. J. M. ADAMS and I. MCQUARRIE, J. Pediat. **12**: 176 (Feb.) 1938.

A 12 year old girl had severe anemia. The blood picture closely resembled that of pernicious anemia in the adult, and there was absence of free hydrochloric acid in the gastric contents. She was treated by parenteral administration of liver extract (the antipernicious anemia factor). Complete recovery followed this treatment. During convalescence polyphagia and obesity developed, the basal metabolic rate dropped, a dextrose tolerance test showed a high level of sugar in the blood, and moderate osteoporosis of the bones appeared. These changes suggested the adrenal cortex syndrome or Cushing's pituitary basophilism in an early stage. The signs suggestive of endocrinopathy disappeared during the following year. The authors believe that the patient probably suffered temporarily from a lack of the intrinsic antianemic factor, although special tests for this intrinsic substance could not be carried out. The underlying pathogenesis of the anemia is obscure but may be explained by an acute febrile illness which preceded the anemia and which may have been responsible for a transient functional disturbance of the mechanisms normally responsible for the production of both free hydrochloric acid and the intrinsic antianemic factor. Whether the disturbance in body metabolism following recovery from the anemia is related to the response of the hemopoietic system is problematic. Insufficient data are available for a satisfactory interpretation in this case, although in the literature there is some evidence which points to an intermediary effect of the anterior pituitary on hemopoiesis.

RAUH, Cincinnati.

EFFECT OF CHOLINE ON PRODUCTION OF EXPERIMENTAL ATHEROSCLEROSIS IN RABBITS. A. STEINER, Proc. Soc. Exper. Biol. & Med. **38**:212 (March) 1938.

Feeding of choline to rabbits which were given extra cholesterol in the diet did not prevent the hypercholesteremia which occurs when the cholesterol intake is increased. There was a delay in the development of atheromas in the aorta in the animals which had been given choline, but the atherosclerosis was not prevented in these cholesterol-fed rabbits.

HANSEN, Minneapolis.

ACUTE LEUKEMIA IN CHILDHOOD: AN ANALYSIS OF SIXTEEN CASES. L. M. SIMONSON, Wisconsin M. J. **37**:110 (Feb.) 1938.

In most instances of leukemia in childhood the condition is of the lymphoblastic type and acute in course. Some instances of the myelogenous or of the monocytic type have been reported. The diagnosis is frequently erroneous because of the instability of the child's hemopoietic system.

Sixteen cases of leukemia in children aged from 10 months to 13 years who were admitted to the Wisconsin General Hospital over a period of ten years are reported. The average age was 7 years. The distribution as to sex was about equal. The chief complaints were: weakness in 10, pallor or anemia in 10, petechia or bleeding in 7, pain in extremities in 5, swollen glands in 3 and anorexia, vomiting, fever, abdominal mass, jaundice, cardiac complaint, paralysis and cough in some instances.

The course of the disease was followed through to death in 15. The shortest period of illness was two months and the longest eight and a half months, with an average of four and a fifth months. Seven of the series gave an account of, or had, pain, swelling or tenderness in joints or bones. Heart murmurs were heard in 12, particularly in those who were anemic. Of the 6 for whom roentgenograms were made, 2 showed fuzziness of the skull, 1 a lesion in a diaphysis, 1 infiltration of the femur and another some intracranial calcification. Studies of the blood showed an average hemoglobin content of 38 per cent and a red cell count of 2,350,000. Fifteen of the children had from moderate to marked reduction in the number of platelets. A normal white cell count was common; all but 3 of the children had a total count below 10,000 at some time while in the hospital; the highest count was 725,000. Changes could not be correlated with the progress of the condition. Adenopathy, splenomegaly and enlargement of the liver were found to varying degrees in almost every case.

Treatment affected the course but little in these cases. Roentgen radiation, often believed helpful, seemed to be harmful. JANNEY, Wauwatosa, Wis.

STUDIES IN ANAEMIA OF INFANCY AND CHILDHOOD. L. G. PARSONS, E. M. HICKMANS and E. FINCH, Arch. Dis. Childhood **12**:369 (Dec.) 1937.

This is a study of the effect of diets deficient in iron on the size of red blood cells in rats and in the production of microcytic hypochromic anemia in their offspring, with the following results:

1. A special iron-deficient solid diet has been devised which when fed to rats results in the development of polycythemia and microcytosis although the hemoglobin remains normal—findings which it is suggested are the first step in the production of iron deficiency anemia.
2. The offspring of such rats acquire in the lactation period anemia greater than the physiologic anemia of infancy, microcytic in type.
3. If these young rats after weaning are fed the special diet microcytosis persists, but polycythemia develops, and the hemoglobin becomes normal.
4. If the diet of these young rats after weaning is restricted to milk the anemia becomes progressively worse and the cells smaller and less numerous than those in the group receiving the special diet.
5. The cells can be restored to normal size by the administration of adequate amounts of iron and a trace of copper.
6. Rats fed the diet for one generation can produce and rear their litters fairly well, but the reproductive powers of the succeeding generation fed the same diet are greatly diminished; the young are reared with difficulty, are subnormal in weight and size and show even more pronounced anemia than the preceding generation.
7. The analogies between these findings and certain clinical conditions in the human mother and infant are pointed out.
8. The findings support the suggestion that the infants of women whose diets during pregnancy are low in iron or who suffer from iron deficiency anemia may show congenital nutritional anemia. KELLY, Milwaukee.

PHYSIOTHERAPY AND PERIPHERAL CIRCULATION. F. NAGELSCHMIDT, Brit. J. Phys. Med. **1**: 44 (Feb.) 1938.

Nagelschmidt discusses the effect on peripheral circulation of massage, manipulation, ultraviolet irradiation, diathermy, roentgen therapy and use of radium. The article is a review of what is commonly known. In the comment it is shown that if results worth while are to be obtained a physician trained in physical therapy should direct and plan the treatment rather than a masseur or a physiotherapist.

HARTMAN, Cleveland.

ANEMIA CURED BY SPLENECTOMY. P. M. ANDERSON, M. J. Australia **1**:385 (Feb. 26) 1938.

Anderson reports that acquired erythronoclastic (hemolytic) anemia in a 2 year old child was cured by splenectomy. The disease was characterized by persistently low total red cell and reticulocyte counts, evidence of accumulation of the products of red cell destruction in serum and urine, absence of fragility and sperocytosis of the red cells, failure of response to liver therapy and normality of white blood cells.

GONCE, Madison, Wis.

TWO CASES OF MONOCYTIC LEUKAEMIA. G. H. NEWNS and A. G. SIGNY, Proc. Roy. Soc. Med. **31**:364 (Feb.) 1938.

The first patient was a child 2½ years of age. The results of examination and the full blood counts are given. Six days after admission the child died from edema of the larynx. Permission for an autopsy was refused, but biopsy of the liver, spleen and a lymph node was performed. There was leukemic infiltration of all these organs, the predominating cell being the monocyte.

The second patient was a child 2 years old. She became progressively worse and died ten days after admission. Permission for an autopsy was granted, and a full description of the organs is given.

WILLIAMSON, New Orleans.

CONGENITAL VARICOSE VEINS OF FOREARM. E. H. JEBENS, Proc. Roy. Soc. Med. **31**:545 (March) 1938.

The patient at the age of 4 years showed several small bluish swellings over the dorsal aspect and over the ulnar border of the lower part of the left forearm and also over the dorsum of the fingers and hand. The swellings were firm and did not disappear when the arm was raised. There was no pain and no difference in temperature between the two sides. All the joints were normal. The swellings were first noticed fourteen days after birth. On operation a small cyst containing dark blood was removed from the dorsal aspect of the wrist. It did not appear to be in continuity with a vein of any size, and there was no bleeding after its removal. The pathologist's report stated that the principal tissue seemed to be angiomatous and very degenerate. There was no evidence of sarcoma nor any inflammatory basis for the subcuticular hemorrhage.

WILLIAMSON, New Orleans.

THE LEUKEMIAS. M. REY and A. A. DIHARCE, Rev. méd. latino-am. **23**:49 (Oct.) 1937.

The pathology and the classification of the leukemias are discussed and 4 illustrative cases are described in detail.

DWYER, Kansas City, Mo.

A THROMBOPLASTIC FORM OF MORBUS MACULOSUS WERLHOFI. I. SCHARFF, Med. Klin. **34**:80 (Jan. 21) 1938.

Although splenectomy is usually curative in cases of Werlhof's disease, failures have been reported. Scharff reports a case in a 4½ year old child in which

medical treatment (including vitamin C therapy) and splenectomy failed to produce improvement. The only change in the blood picture following splenectomy was an enormous increase in the number of normoblasts; the platelet count remained around 10,000. A smear of sternal marrow revealed an abundance of megakaryocytes but the same thrombopenia as in the peripheral blood. Apparently the megakaryocytes lacked the ability to form thrombocytes. Scharff recommends sternal puncture in extreme cases of thrombopenia to determine the advisability of splenectomy.

SIEMSEN, Chicago.

FETAL ENDOCARDITIS. J. ÁBRAHÁM, Orvosi hetil. **81**:887 (Aug. 28) 1937.

A newborn infant of a 21 year old primipara died three days after birth with asphyctic symptoms. The infant did not show decided alterations: The skin was a little cyanotic, and the sounds over the heart were clear after birth, without any murmur; the last day one could hear a sharp systolic murmur, which was present with the same intensity over every part of the heart. The postmortem examination showed that the heart was greatly enlarged, especially the right ventricle. One could find on the bicuspid valves and especially on the valves of the aorta endocarditic alterations. The mother had not suffered any infectious diseases during her pregnancy; her heart did not show any pathologic alterations; the birth and the recovery were normal. One could not determine the cause of this fatal endocarditis, but from the fact that calcifications could be found in the degenerated muscles of the left ventricle one can suppose that the process had been present for a long time.

GÖTTCHE, Budapest, Hungary.

LATENT EDEMA OF CARDIAC ORIGIN IN INFANTS. P. KISS, Orvosi hetil. **81**:1309 (Dec. 25) 1937.

It is well known that infants in the initial periods of most acute diseases lose weight and that when the fever stops and recovery begins the loss of weight stops and the weight curve begins to rise. One can find cases in which in spite of severe illness and insufficient nutrition a loss of weight does not occur, rather a gain. This gain is caused, according to Kiss, by an edema of cardiac origin. In the years 1931 to 1932, during an epidemic of grip, in 14 of 89 infants this phenomenon was observed. This latent cardiac edema does not always cause a gain in weight; it can also occur that the infant keeps its weight during the first period of the illness, and the weight starts to sink only when recovery begins. Cessation of this cardiac edema can be hastened by means of digitalis.

GÖTTCHE, Budapest, Hungary.

INTERPOLATED EXTRASYSTOLE IN CHILDREN. H. MIDUNO, Acta pædiat. japon. **44**:421 (March) 1938.

In a 3½ year old child with arrhythmia electrocardiographic studies revealed interpolated extrasystole in addition to the ventricular extrasystole with compensatory pause. Both systoles were worse during the night, with a diminution in the pulse rate, suggesting vagotony as the underlying cause. Quinidine appeared to have a temporary beneficial effect.

KATO, Chicago.

A CASE OF NIEMANN-PICK DISEASE. S. KATO, Acta pædiat. japon. **44**:533 (April) 1938.

A case of Niemann-Pick disease in a 9 month old girl is reported. The beginning of the disease was clearly traced to the age of 3 months. The typical symptoms, generalized lymphadenopathy and a protuberant abdomen due to splenohepatomegaly, were noted. Dried splenic substance contained on chemical analysis 3.08 per cent lecithin.

KATO, Chicago.

CARBONIC ACID CONTENT OF BLOOD SERUM AND OF SPINAL FLUID OF NORMAL INFANTS. T. TANAKA and S. OKUDA, J. Orient. Med. **27**:971 (Dec.) 1937.

In the blood of 25 of 26 normal infants the authors found from 38.96 to 58.42 volumes per cent of carbon dioxide, with an average of 48.7 volumes per cent. In 9 infants with jaundice the carbon dioxide content of the blood averaged 46.4 volumes per cent, showing thus a tendency to be lower than in nonicteric infants (average, 49.8 volumes per cent). The average carbonic acid content of the cerebrospinal fluid in 26 normal infants was found to be 48.6 volumes per cent and that of infants with jaundice 47.6—a difference of only 1. There was no significant deviation in the carbon dioxide content of the blood as compared with that of the cerebrospinal fluid.

KATO, Chicago.

PURPURA HAEMORRHAGICA AND SPLENECTOMY. S. KROONENBERG, Maandschr. v. kindergeneesk. **6**:431 (Aug.) 1937.

Kroonenberg describes a case of acute thrombocytopenic hemorrhagic purpura (Morbus maculosus Werlhofii) in a girl of 14 years. The bleeding time was increased; there was insufficient retraction of the blood clot, and bleeding occurred in the skin and different mucosae. Meningeal and retinal hemorrhages, usually considered as very rarely associated with this disease, necessitated splenectomy. After this, recovery was delayed, and the patient remained in a very critical condition for ten days. Then the number of platelets began to increase, and the patient soon felt improved and remained well during the two years that this observation lasted. Blood transfusions seem to have been life saving, after the splenectomy. Different medications recently advised are discussed.

VAN CREVELD, Amsterdam, Netherlands.

TWO CASES OF ANOXEMIA. J. H. P. JONXIS, Maandschr. v. kindergeneesk. **7**:58 (Nov.) 1937.

In 2 cases of anoxemia Jonxis has determined the oxygen saturation of the arterial blood after a method of his own. In the first instance, a girl of 6 years was suffering from exudative miliary tuberculosis and had a lung nearly totally filled with exudate. The oxygen saturation of this patient's blood was only 50 per cent. The dissociation curve of the blood deviated, however, from normal, and therefore the oxygen tension of the tissues could still be favorable. In the other case, a baby of some months appeared to have a transposition of the large vessels with open ductus Botalli, and during life no oxygen could be found to be present in the arterial blood. Jonxis assumes that in this case oxygen was transported by means of the glutathione.

VAN CREVELD, Amsterdam, Netherlands.

INFLUENCE OF BODY POSTURE ON THE FORM OF THE ELECTROCARDIOGRAM. A. D. ERKELENS, Nederl. tijdschr. v. geneesk. **81**:4557 (Sept. 25) 1937.

Electrocardiograms were taken of 16 patients with cardiac disease and 45 persons with normal hearts, with the subjects in the supine and in the erect position. The changes observed are discussed. There were found, among others, enlargement of P in lead II and in lead III, decrease of RT, enlargement of R with lead III, deepening of ST and decrease of T in all leads.

Attention is drawn to the discordance between QRS changes and T changes in many cases, which disproves the explanation that T changes result from a change in the site of the heart.

Arguments are brought forward in favor of the decrease of T in leads II and III being the result of a defect in the supply of blood to the heart muscle in the erect position. This decrease was found in healthy as well as in diseased subjects and, in the author's opinion, cannot be used as a diagnostic sign of myocardial disease. The type of body build appeared to have a distinct influence.

VAN CREVELD, Amsterdam, Netherlands.

HYPNOSIS AS A TREATMENT IN ESSENTIAL HYPERTENSION. B. STOKVIS, Nederl. tijdschr. v. geneesk. **81**:5676 (Nov. 27) 1937.

The reaction of the blood pressure of patients with essential hypertension on hypnotic treatment is dependent on four criteria, which are discussed in detail. The patients who are suggestible and hypnotizable, who have good renal activity and who are classified in the group of the sentimental temperament in the sense of Heymans' typology are especially suitable for hypnotic treatment. There is a difference in effect between subjective and objective phenomena: While the decrease in blood pressure, which is greater in the systolic than in the diastolic blood pressure, continues only for several weeks, the amelioration of the complaints lasts for longer than half a year.

VAN CREVELD, Amsterdam, Netherlands.

Diseases of Nose, Throat and Ear

BLOOD CULTURES AFTER TONSILLECTOMY. H. SOUTHWORTH and C. G. FLAKE, Am. J. M. Sc. **195**:667 (May) 1938.

The blood cultures of 22 patients in whom tonsillectomy was performed were analyzed. Of the preoperative cultures, 3 (13.6 per cent) showed growth, and of the postoperative, 4 (18.2 per cent), and in no case was there growth in both preoperative and postoperative cultures of the same patient. No constant relation could be made out between the clinical course and the presence or the absence of a positive culture. The authors feel that the evidence so far in their own and other cultures recorded in the literature does not establish the fact that bacteremia occurs after tonsillectomy in any significant number of cases.

HENSKE, Omaha.

ELECTROLYTE BALANCE OF THE BLOOD IN MÉNIÈRE'S DISEASE. J. H. TALBOTT, M. R. BROWN, F. S. COOMBS and W. V. CONSOLAZIO, Proc. Soc. Exper. Biol. & Med. **38**:421 (April) 1938.

Diets in which sodium is low have been shown to be effective in the treatment of Ménière's disease. No change in the content of sodium or of total fixed base in the serum has been found. During the symptom-free phase, addition of sodium salts does not precipitate attacks. Increasing the potassium intake but keeping the sodium content normal brings about an alleviation of symptoms comparable to that obtained with the low sodium diet.

HANSEN, Minneapolis.

ACUTE SINUSITIS IN CHILDREN. G. S. FITZ-HUGH, Virginia M. Monthly **65**:251 (May) 1938.

The anatomic structure and development of the nasal accessory sinuses in infants and young children are reviewed. Some degree of sinusitis occurs with practically every cold. Anatomic obstruction to drainage, allergic rhinitis and forceful blowing of the nose may be factors in the development of acute sinusitis. A child may have acute sinusitis without a very evident discharge. Edema and reddening of the eyelids are the most frequent symptoms. Transillumination and roentgen examination are important in diagnosis. Trauma, abscessed teeth, infections of the eyelids and face and thrombosis of the cavernous sinus must be differentiated.

Conservative treatment is aimed at keeping nasal passages and the ostia of the sinuses open. Nasal instillations or sprays of from 1 to 3 per cent ephedrine in oil followed by from 5 to 10 per cent mild silver protein are helpful. Rest in bed, a warm environment and a proper diet, with adequate supply of fluids and vitamins, should be provided. If progress is not favorable, a minor or a major surgical operation may be needed, with the object of obtaining adequate drainage with the least possible trauma. Proptosis and fixation of the globe suggest orbital abscess. Other complications to be feared are septicemia, osteomyelitis, meningitis, abscess of the brain and thrombosis of the cavernous sinus.

Fitz-Hugh reports 30 cases in children aged from 1 to 12 years. In 20 of these cases the chief complaint was edema of the lids. Two deaths occurred, each from abscess of the brain and meningitis.

Fitz-Hugh urges that acute rhinitis in children be considered as potential acute sinusitis and that local treatment be directed toward relieving nasal congestion. Surgical intervention other than of a minor type should be practiced only as the last resort and to prevent the development of more serious complications.

The follow-up care after an attack of acute sinusitis is important.

STONE, Richmond, Va.

INFRA-RED RAYS. F. H. HUMPHRIS, Brit. J. Phys. Med. **1**:118 (April) 1938.

In a long consideration of infra-red irradiation Humphris mentions its usefulness in the treatment of otitis media. He describes a special type of lamp which can be strapped on the head.

HARTMAN, Cleveland.

A NOTE ON THE INCIDENCE OF SINUSITIS IN CHILDREN. J. H. EBBS, Brit. M. J. **1**:385 (Feb. 19) 1938.

This report is based entirely on postmortem observation of sinuses in children of the ages from birth to 14 years who had died from a variety of medical and surgical conditions. The frontal sinus was not included in the survey.

Of 496 children examined, 152 were found to have infections of the sinuses other than the frontal. This gives an incidence of 30.6 per cent. It is stated that 32.6 per cent of 331 infants under 12 months of age and 33.3 per cent of 60 children in the second year of life had infected sinuses. The maxillary antrum furnished the largest incidence of infection—29.5 per cent. The sphenoid sinus came next, with 15.4 per cent; then the ethmoid, with 13.74 per cent. In the whole group, the middle ear was involved in 56.4 per cent.

ROYSTER, Charlottesville, Va.

INFLAMMATION OF THE NASAL ACCESSORY SINUSES IN CHILDHOOD. G. FABINYI, Orvosi hetil. **81**:1219 (Dec. 4) 1937.

Most inflammation of the nasal accessory sinuses in children—especially the chronic inflammations—are not expressed in symptoms. Therefore the control of these children by rhinolaryngologists is important. In infants and little children it is mostly the ethmoid cells and the maxillary sinuses that become diseased. Roentgen examination is of the greatest value in cases of inflammation of maxillary sinuses. The most frequent and most serious complications are to be found in the orbits. They occur mostly in cases of scarlet fever (86 per cent). Fabinyi observed 66 similar cases and lost the patient in only a single case. Operative intervention is required only when conservative treatment proves unsuccessful and when complications threaten.

GÖTTCHE, Budapest, Hungary.

Diseases of Lungs, Pleura and Mediastinum

ATELECTATIC BRONCHIECTASIS: RECOVERY. A. W. FRANKLIN, Proc. Roy. Soc. Med. **31**:354 (Feb.) 1938.

Atelectatic bronchiectasis is reported in a boy aged 7 years. His previous history, the results of physical examination and of investigations, photographs of roentgenograms of the chest taken before and after injection of iodized poppyseed oil 40 per cent and the course of his illness until he was discharged well are given in the report.

WILLIAMSON, New Orleans.

PNEUMONIA WITH UNUSUAL FEATURES IN AN INFANT. R. A. PELLEW, Proc. Roy. Soc. Med. **31**:369 (Feb.) 1938.

A baby of 15 months was admitted to a hospital with the complaint of cough, dyspnea and increasing pallor. The chest showed diminished movement on the

left side, with dulness to percussion and two distinct areas of consolidation, the impression being that these areas were of different ages. The diagnosis was therefore made of pneumonia migrans. The child progressed satisfactorily for fourteen days. The white cell count at about this time was 13,800, and the temperature began to rise. One month later it was noticed that the fingers had begun to club, while the temperature was swinging, and the white cell count had risen to 27,000. Two cubic centimeters of pus was withdrawn from the eighth intercostal space. A roentgenogram of the chest, taken with the child in an upright position, showed three distinct cavities in the lungs, two of these having fluid levels. Aspiration from the upper cavity was carried out every second day, with removal of about 20 cc. of pus, which on being cultured showed a pure growth of pneumococci.

WILLIAMSON, New Orleans.

RECURRENT LOBAR COLLAPSE. D. GAIRDNER, Proc. Roy. Soc. Med. **31**:562 (April) 1938.

A boy of 8½ years had had an attack of bronchopneumonia at the age of 3 years. He was first seen at 4 years. He had had cough intermittently ever since the attack. From August 1933 to December 1935 he had frequent attacks of cough, with dulness and rales over the base and middle lobe of the right lung, and roentgen examination at these times showed an opacity over these areas and calcified glands near the right hilus. Then for two years the child remained well except for occasional coughs, and the lungs remained free from abnormal sounds. In 1937 the child was seriously ill for one week with cough and noisy breathing. Roentgen examination at this time showed the middle and lower lobes of the right lung opaque, the appearance resembling that in the previous attacks. The left lung showed a pneumonic process. A month later roentgenograms showed both lungs clear.

WILLIAMSON, New Orleans.

A PRELIMINARY REPORT ON THE VALUE OF STOCK VACCINE IN THE TREATMENT OF PNEUMONIA. J. H. BOLTON, Quart. J. Med. **7**:171 (April) 1938.

Bolton administered a mixed vaccine to each of 32 patients with pneumonia within three days after the onset. Fifty-nine patients served as controls. The 91 patients were admitted to the Royal Melbourne Hospital, Australia, during the period from May 1936 to July 1937. The mixed vaccine contained 600,000,000 organisms per cubic centimeter, equally partitioned among 6 different types, i. e., pneumococcus types I, II and III, a strain representative of type IV, a strain representative of Streptococcus, and Micrococcus catarrhalis.

Bolton maintains that the results reported are statistically valid and that they appear to support the findings of Wynn, an advocate of vaccine therapy for pneumonia. He concludes that vaccine therapy appears to reduce the duration of uncomplicated pneumonia by an average of three days. Recovery within five days after the onset appears to be much more likely if vaccine has been given.

BRADFORD, Rochester, N. Y.

CHRONIC MEDIASTINAL-HILAR LYMPHADENOPATHY IN CHILDHOOD. D. ELLER, Lattante **9**: 118 (March) 1938.

This article is a review of the symptoms, pathologic features and diagnosis of childhood tuberculosis.

HIGGINS, Boston.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

A CASE OF PEPTIC ULCER IN A CHILD FOLLOWING BRAIN INJURY. F. R. VANZANT and J. A. BROWN, Am. J. Digest. Dis. **5**:113 (April) 1938.

Vanzant and Brown report a case of duodenal ulcer occurring twenty days after an injury to the head (concussion). The patient was 11 years of age. The duodenal ulcer was shown by fluoroscopic examination after clinical symptoms suggested peptic ulcer. Blood was present in the stools.

The relationship between intracranial lesions and the presence of gastrointestinal ulceration is brought out (Cushing's view).

The question of compensation and the possibility of recurrence comes up in these cases of accidental peptic ulcer. Such ulcers practically never recur, and the tendency is toward rapid healing.

MORRISON, Savannah, Ga.

CHOLECYSTITIS IN CHILDHOOD. H. LOWENBURG JR. and A. G. MITCHELL, J. Pediat. **12**:203 (Feb.) 1938.

Eight cases of cholecystitis in children observed at the Children's Hospital, Cincinnati, and at the Cincinnati General Hospital during the past twelve years are presented. The commonest symptom was abdominal pain, located usually in the hypochondrium, particularly on the right side. The pain varied in different children from a dull ache to an intense cramplike sensation. Nausea usually occurred, frequently with vomiting, and sometimes fever to a varying degree. Examination demonstrated tenderness and rigidity of the abdomen, more marked on the right side and usually in the upper quadrant. Jaundice was present in some patients but in more of them was absent. A tender mass in the region of the gallbladder was palpable in some. In some the liver was slightly enlarged. Moderate leukocytosis was usually found. In 5 of the patients there was an associated infection of the upper respiratory tract. In 2 patients a chronically diseased appendix was found at operation. One patient had a typhoid bacillus infection of the gallbladder. Another had Lamblia intestinalis in the stool and in the biliary returns. Biliary drainage was used for diagnostic purposes in 2 patients. One of these was cured by this procedure. Oral cholecystographic study was succesful in yielding a diagnosis of cholecystitis in 3 cases.

The authors believe that cholecystitis is not infrequently the cause of unexplained abdominal pain in children and that it is too often overlooked, the pain being attributed to mild gastroenteritis, indigestion or subacute appendicitis.

RAUH, Cincinnati.

A STUDY OF VISCERAL PAIN AS RELATED TO THE BILIARY TRACT. G. S. BERGH and J. A. LAYNE, Proc. Soc. Exper. Biol. & Med. **38**:44 (Feb.) 1938.

Fifteen patients with choledochotomy and intubation of the common bile duct were subjected to sudden distention of the bile ducts with injections of saline solution at pressures of from 50 to 100 cm. of water. In each instance the pain produced was similar to that experienced previously and was either a deep epigastric pain or a pain in the right upper quadrant of the abdomen, and in 7 cases the pain was also radiated to the right subscapular or interscapular region. Gradual distention of the ducts with water up to 100 cm. caused no symptoms.

HANSEN, Minneapolis.

EFFECTS OF INTRAVENOUS INJECTIONS OF ACACIA ON CERTAIN FUNCTIONS OF THE LIVER. W. K. HALL, Proc. Soc. Exper. Biol. & Med. **38**:46 (Feb.) 1938.

Following intravenous injections of acacia in dogs, the following observations were made: (1) marked impairment of galactose tolerance and some impairment of dextrose tolerance, (2) definite decreases in serum protein and (3) very low levels of plasma fibrinogen. Thus, the deposition of acacia in the dog's liver produces impairment of hepatic function in the metabolism of carbohydrate and plasma protein.

HANSEN, Minneapolis.

TREATMENT OF INFANTILE PYLORIC STENOSIS BY ANTISPASMODICS. J. V. BRAITHWAITE, Brit. M. J. **1**:334 (Feb. 12) 1938.

It is difficult to appraise this article in the light of the American conception. It is doubtful whether there is a sharp distinction made between spasm and

stenosis. The author's diagnosis in each case depended largely on roentgenographic data, projectile vomiting and a palpable pyloric tumor. The abstracter suggests that a number of the infants treated with antispasmodics for stenosis had what the American group would call pyloric spasm rather than hypertrophic pyloric stenosis.

ROYSTER, Charlottesville, Va.

PHYSIOLOGIC AND BIOCHEMICAL CONSIDERATIONS OF HEPATIC FUNCTION IN HEALTH AND DISEASE. I. MAXWELL, M. J. Australia **1**:511 (March 19) 1938.

Maxwell discusses the following functions of the liver: storage of glycogen, desaturation of fats, deaminization of amino acids, secretion of bile salts, excretion of bile pigments, formation and destruction of red corpuscles, detoxication of products of putrefaction of protein, formation of fibrinogen, storage of the hematinic principle and storage of vitamins. Emphasis is placed on: (1) the futility of any attempt to increase the glycogen content of the liver by rectal administration of dextrose in man; (2) the importance of bile salts as cholagogues and in aiding the solution of cholesterol in bile; (3) the intensive storage of hematinic principle in the liver; (4) the important role that choline may play in the future therapeutic control of the fat content of the liver.

GONCE, Madison, Wis.

HIRSCHSPRUNG'S DISEASE. W. M. FELDMAN, Proc. Roy. Soc. Med. **31**:366 (Feb.) 1938.

Hirschsprung's disease is reported in a boy aged 11 years. The history of the illness, the results of physical examination and of investigations, the treatment and the operation, which was performed under spinal anesthesia, are all given in the report.

WILLIAMSON, New Orleans.

COLITIS ASSOCIATED WITH STRICTURE OF THE RECTOSIGMOIDAL JUNCTION. M. D. RAWKINS, Proc. Roy. Soc. Med. **31**:369 (Feb.) 1938.

A girl aged 8 years had been well until the age of 2 years, when she had an attack of measles (?). For six months she was constipated. Then chronic diarrhea set in, which persisted. In 1935 a diagnosis of chronic colitis was made. On admission to the hospital she appeared to be happy and healthy. A stricture was felt a finger's length from the anal orifice (per rectum). Sigmoidoscopic examination disclosed a stricture centrally situated, with an orifice the size of a lead pencil. The wall was smooth and tough. The stricture was situated about 4 inches (10 cm.) from the anus. Roentgenologic examination showed a stricture at the rectosigmoid junction.

WILLIAMSON, New Orleans.

HEPATOMEGALY IN AN INFANT; VON GIERKE'S DISEASE. G. H. NEWNS, Proc. Roy. Soc. Med. **31**:546 (March) 1938.

An infant of 6½ months was admitted to the hospital on account of dyspeptic vomiting. The only abnormal sign found was enlargement of the liver. The family history and the results of all the investigations are given in this report.

WILLIAMSON, New Orleans.

HEMORRHAGIC, HYPERTROPHIC PYLORIC STENOSIS. L. RIBADEAU-DUMAS, J. CHABRUN and MME. LOEWE-LYON, Rev. franç. de pédiat. **13**:542, 1937.

The authors report a case of pyloric stenosis in which hematemesis was a prominent feature both before and after operation. When it occurred after operation it seemed to be the culmination of several days of disturbance during which there was vomiting of much mucus with the feeding. On the twenty-fourth day the child was operated on and on the fifty-sixth day presented the

last episode of hemorrhage, following which recovery was complete. The authors think the hemorrhage from the gastric mucosa was probably associated with stasis, although the possibility of gastric ulcer must be kept in mind in the presence of this symptom.

LESLIE, Evanston, Ill.

ANOREXIA IN THE INFANT AND IN THE YOUNG CHILD. M. SCHACHTER-NANCY and H. FEINSTEIN, Lattante **9**:41 (Jan.) 1938.

Anorexia may be divided into two types (1) essential or mental and (2) symptomatic or secondary. Symptomatic anorexia may be subdivided into seven types according to causes, as follows:

1. General causes (debility, prematurity, hyperexcitability)
2. Infectious causes
3. Digestive causes (dietary errors, avitaminosis)
4. Pathologic states of the mouth and pharynx (stomatitis, dentition)
5. Nervous causes (fatigue)
6. Various toxic causes (parasites)
7. Medicamental causes (prolonged and excessive use of drugs)

When essential anorexia occurs, there have been grave faults in the educational handling of the child. The patient is usually the only child, the smallest child or the most loved child of the family. Therapy should take account of the educational faults; here medicopsychologic hygiene and a medicopedagogic consultation often help.

HIGGINS, Boston.

ANOREXIA IN INFANCY. C. INCLAN and V. SANTAMARINA, Arch. de med. inf. **7**: 233 (April-June) 1938.

The authors divide anorexia of infancy into two main types: 1. False anorexia. Under this they list such cases as malformation of the digestive tract, obstetric injury, encephalopathy, retropharyngeal abscess, adenoids and faulty dentition. 2. True anorexia. Under this they list as causes digestive factors, elective propensities, debility, hereditary difficulties and mental states.

Some of the findings in older children are of interest: Of 330 children studied, 52 per cent had hypertrophied tonsils and adenoids; 29 per cent had positive Mantoux reactions, 40 per cent had intestinal parasites, 36 per cent had positive Sellek-Frade (analogous to Kahn and Meinicke) reactions, 20 per cent had extensive dental caries and 5.4 per cent showed various other ailments.

SANFORD, Chicago.

SPASTIC ILEUS. LICHTI, Monatschr. f. Kinderh. **73**:63 (April) 1938.

Lichti reports that 2 infants died of obstinate vomiting and constipation due, he thinks, to a spastic ileus. The report is not convincing.

GERSTLEY, Chicago.

ACUTE YELLOW ATROPHY OF THE LIVER DEVELOPING IN THE COURSE OF ACUTE DYSPEPSIA. Y. NAGAI, Acta pædiat. japon. **44**:116 (Jan.) 1938.

In a boy 1½ years old who was being treated for acute dyspepsia a sudden enlargement of the liver was noted, the liver margin reaching approximately 10 cm. below the costal margin. The enlargement was accompanied by such alarming symptoms as chills, high fever, salivation, vomiting, convulsion and stupor. A long-continued presence of leucine crystals in the urinary sediment was of especial interest. Under symptomatic treatment a complete recovery was effected.

KATO, Chicago.

THE PHYSIOLOGIC MECHANISM OF THE DECREASE OF ACIDITY IN GASTRIC CONTENTS. W. N. BOLDYREFF and W. F. MARTIN, Acta med. Scandinav. **95**:151, 1938.

Experiments were done on normal persons, on a patient with pylorospasm and on dogs with Pavlov's pouch.

Neutralization of acid fluids in the empty stomach is rapid, progressive and uniform; it is accomplished without significant dilution, as the chloride ion concentration remains uniform in spite of diminished acidity, and when lactic acid was introduced instead of hydrochloric acid little chloride was demonstrated in the gastric contents, indicating that gastric mucosa does not secrete neutral chloride.

Neutralization occurs from the duodenum, for in the stomach of the patient with pylorospasm and in the stomach pouches of dogs or in a stomach isolated from the intestines it did not occur. Exclusion of saliva by esophageal fistula has no effect on the processes of neutralization.

Pancreatic juice is the most important agent, but if most of the pancreatic juice is removed by a fistula of the main pancreatic duct the neutralization will be accomplished by the intestinal juice and bile.

KAJDI, Baltimore.

Nervous Diseases

RELATION OF LYMPHOCYTIC CHORIO-MENINGITIS TO ACUTE ASEPTIC MENINGITIS (WALLGREN). R. D. BAIRD and T. M. RIVERS, Am. J. Pub. Health **28**:47 (Jan.) 1938.

Baird and Rivers examined spinal fluids and blood specimens from 65 persons suspected of having aseptic meningitis. Further study of the histories disclosed the fact that in 31 of these persons the requirements for a diagnosis of aseptic meningitis were not fulfilled. Spinal fluids and 11 blood specimens were examined for the virus of lymphocytic choriomeningitis; in none of these was virus found. The blood was examined for neutralizing antibodies, and 1 case was found which proved to be an instance of choriomeningitis, and 7 presumptive cases. The authors conclude that aseptic meningitis is not caused by the virus of lymphocytic choriomeningitis in all cases and that the etiologic background of the disease in question is not known. The two conditions cannot be differentiated, but cell counts on the spinal fluid tended to be higher in the cases of lymphocytic choriomeningitis than in the remaining cases studied.

Children and infants are not infrequently attacked by the virus of lymphocytic choriomeningitis.

LIMPER, Louisville, Ky.

TOXIC ENCEPHALOPATHY IN A CHILD FOLLOWING THE INTERNAL ADMINISTRATION OF POTASSIUM CHLORATE AND SULPHARSPHENAMINE. J. GREENGARD, J. Pediat. **12**:197 (Feb.) 1938.

A 4 year old white child was treated for stomatitis by administration of large doses of potassium chlorate and by intramuscular injection of two doses of sulfarsphenamine of 0.2 Gm. each. Subsequently severe toxic encephalopathy developed. The causal relationship of the encephalopathy to the drugs is not proved, but the case is highly suggestive of such a relationship. Greengard considers the toxicology of potassium chlorate and concludes that potassium chlorate should never be administered internally in a child and that its local use should be approached with caution.

RAUH, Cincinnati.

ARTIFICIAL FEVER THERAPY OF SYDENHAM'S CHOREA. H. W. KENDALL and W. M. SIMPSON, Ohio State M. J. **33**:1097 (Oct.) 1937.

Kendall and Simpson subjected 5 patients suffering from Sydenham's chorea to artificial fever therapy using the Kettering hypertherm. All experienced prompt cessation of choreiform movements. None has had recurrence. There were 4 girls and 1 boy. The duration of chorea prior to the administration of

artificial fever ranged from ten days to three weeks in the 4 patients with severe disease, and 1 child had had repeated attacks for one year before artificial fever therapy was given. These patients were given from one to eleven treatments, the average single fever session being three hours, with temperatures from 104 to 105 F. The period of observation extends from six weeks to four and one-half years. In addition to the choreiform movements, 3 patients showed evidence of carditis, as demonstrated by mitral murmurs, electrocardiographic changes and tachycardia. The mitral murmurs disappeared in all after treatment. The normal cardiac rate and rhythm were restored. Two patients had polyarticular arthritis, which also responded promptly to artificial fever. No other form of treatment was employed. All the children tolerated the treatments well, and none was injured in any way.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.]

BLOOD AND SPINAL FLUID MAGNESIUM AND CALCIUM LEVELS IN EPILEPSY AND CONVULSIVE STATES. D. M. GREENBERG and R. B. AIRD, Proc. Soc. Exper. Biol. & Med. **37**:618 (Jan.) 1938.

In 28 subjects suffering from various convulsive states, including 14 with epilepsy, determinations of the plasma, red blood corpuscles, spinal fluid magnesium, serum and spinal fluid calcium and spinal fluid inorganic phosphorus were made. The spinal fluid was collected in the course of encephalographic examinations. No consistent deviations from normal values were found in the types of convulsive states studied.

HANSEN, Minneapolis.

BRAIN ABSCESS. G. HORRAX, Brit. J. Surg. **25**:538 (Jan.) 1938.

Horrax gives a short résumé of various operative procedures for dealing with abscess of the brain. The operative mortality rate for patients with this condition ranges from 22 to 56 per cent. The lower figures in all probability are a summary of only chronic encapsulated abscesses.

Horrax divides brain abscesses into two groups: Group 1 includes acute and multiple (often metastatic) abscesses. These usually have serious pulmonary or systemic complications. In this group the mortality is 100 per cent, either with or without operation. Group 2 comprises chronic single abscesses (usually encapsulated). In this group the total operative mortality is 16.6 per cent. Of the 14 survivors, 5 have certain disabilities as follows: Two have begun to have convulsions. One of these and 2 others have weakness of one arm and leg. The fifth patient has visual acuity reduced to reading large print but gets along well at school.

Horrax believes the operative procedure of choice is marsupialization and describes the technic fully. He states that the mortality rate from tapping is much higher. He has not had enough experience with complete extirpation to draw any conclusions.

SUMMERFELDT, Toronto, Canada.

TUMOR OF THE CEREBELLUM (EPENDYMOGLIOMA) WITH SECONDARY SYNDROME OF SIMMONDS' DISEASE IN A CHILD EIGHT YEARS OF AGE. S. SAMET-MANDELS and K. SCIESINSKI, Rev. franç. de pédiat. **13**:525, 1937.

The authors report a case of tumor of the cerebellum in which the first sign of disturbance was the development of Simmonds' disease. The emaciation progressed to an extreme degree but responded to anterior pituitary extract. Later the child exhibited signs of rapidly increasing intracranial pressure and died. Autopsy revealed a cerebellar tumor which involved the pons and floor of the fourth ventricle. There was also dilatation of the other ventricles, with a cystlike formation of the infundibulum, which had distorted and compressed the anterior lobe of the pituitary gland.

LESLIE, Evanston, Ill.

A Case of Friedreich's Ataxia (?) with Degeneration of the Retina Resembling Amaurotic Family Idiocy. A. B. Fortes, J. de pediat., Rio de Janeiro **4**:377 (Sept.) 1937.

The boy described was 12 years of age, and the symptoms which were typical of the ataxia had begun when he was 13 months old. There were 3 brothers with similar symptoms. There were 3 other children in the family who were normal, but they were by another father, in a second marriage. A colored plate of the fundus is shown. The fundus resembles that of a patient with amaurotic family idiocy.

Sanford, Chicago.

Epilepsy (?) Microcephaly (?) Porencephaly (?) and Agenesis of the Corpus Callosum in an Idiot with Spasmodic Diplegia. I. Cunha-Lopes and A. Borges-Fortes, J. de pediat., Rio de Janeiro **5**:3 (Jan.) 1938.

Photomicrographs of the brain of this 5 year old child are shown. There were also gross anomalies of the myelin fibers of the extrapyramidal centers. The authors make some interesting generalizations on these conditions as a cause of epilepsy.

Sanford, Chicago.

Encephalitis and Papilledema. F. Langsteiner, München. med. Wchnschr. **84**:406 (March 12) 1937.

The frequent occurrence of papilledema in encephalitis lethargica of von Economo has not been appreciated. Langsteiner cites the case of an 11 year old boy who had an afebrile illness beginning with diplopia, headache, transient right-sided hemiparesis and involvement of the lower branches of the right facial nerve. The cerebrospnial fluid was normal. Later there was also paresis of the left sixth cranial nerve. There was bilateral papilledema, which reached 3 diopters. In a month all the symptoms, as well as the papilledema, had disappeared. An examination six years later revealed no evidence of his previous illness. At the onset of the illness the papilledema, normal spinal fluid and absence of fever led to the diagnosis of tumor of the brain. However, the subsequent course showed that this diagnosis was incorrect.

Langsteiner describes 2 more cases to show that papilledema occurs in acute inflammatory conditions of the central nervous system. The papilledema recedes at the same time that the other symptoms abate. Prolonged observation is frequently necessary to rule out tumor of the brain or multiple sclerosis, for the clinical picture does not always permit a satisfactory differential diagnosis.

Brahdy, Mount Vernon, N. Y.

A Case of Arsphenamine Encephalitis. T. Takabayashi, Acta pædiat. japon. **44**:341 (March) 1938.

A girl 11 years 8 months old was treated by a combination of arsphenamine and preparations of mercury. One hour after the second injection of arsphenamine she suddenly complained of headache, nausea and general malaise. The temperature rose to 39.7 C. (103.5 F.); epileptiform spasticity and intermittent convulsions followed, and the patient fell into a coma. Flushing of the face, spasticity of the limbs and jaws, rolling up of the eyeballs, pupillary dilatation, loss of the light reflex, acceleration in breathing and rapid pulse also developed. Death occurred nineteen hours after the onset of the symptoms. Postmortem examination revealed no gross pathologic change other than evidence of hemorrhagic encephalitis, consisting of changes in the capillary walls of the brain, infarcts, hemorrhages into the lymph spaces around the blood vessels, edema of the perivascular tissue and necrosis.

Kato, Chicago.

A Case of Partial Absence of the Corpus Callosum. T. Hiresaki, Psychiat. et neurol. jap. **41**:85 (Nov.) 1937.

Hiresaki reports a case of partial absence of the corpus callosum in a child aged 8 years who died of pulmonary tuberculosis. Examination revealed horizontal and vertical nystagmus, contracture of the lower extremities, inability to stand or walk, rigidity of the entire body, generalized convulsions at times and a Babinski sign bilaterally. The patient was mentally deficient and indifferent to external stimuli. The brain was small and showed partial loss of the corpus callosum, severe decrease in the white matter, with poor development of the centrum semiovale, marked internal hydrocephalus and a small striatum and thalamus. Microscopic study revealed a well developed cortex; cortical layers II, III and V were poor in cells. The corpus callosum was very small and poor in fibers.

Alpers, Philadelphia. [Arch. Neurol. & Psychiat.]

Psychology and Psychiatry

References to Sex Organs and Functions in Speech Production of Two Preschool Children. A. A. Low, Arch. Neurol. & Psychiat. **39**:519 (March) 1938.

Low attempted to determine the sex interest of children by having two mothers record the daily utterances of their children over a period of two years. It was found that the children talked and asked questions about the other parts of the body as much or more than they did about the genital and anovesical sphere. Low states that no conclusions could be drawn from the observations. Although it was an objective study, a large number of factors were not under control.

Beverly, Chicago.

The Neuro-Psychological Basis of Conduct Disorder. R. G. Gordon, Edinburgh M. J. **45**:43 (Jan.) 1938.

In this Morrison Lecture Gordon, physician at the Royal United Hospital, Bath, England, discusses emotional disturbances. Among these, he comments on disorders of conduct resulting from encephalitis and chorea, especially in children. He believes that the inflammatory changes at the beginning of the encephalitis are followed by vascular lesions which interfere with normal control of the cortex. This upsets the physiologic relation of the cortex, thalamus and hypothalamus. The lesions which are scattered through the cortex are responsible for the outbursts of temper, the tendency to mischievous behavior and the alterations in the affections. These manifestations are entirely different from the child's normal conduct, which is purposeful and calculated. The changes in personality are most marked when the initial illness has been severe.

In chorea there are not uncommonly disorders of behavior, though not severe. Choreic children are said to be jerky in mind also. There have been toxic changes in the brain, which may be regarded as organic. The brain has not been invaded by bacteria, but infection has been present in other organs. From a case in which an autopsy was made it was learned that there had been definite interference with general cortical control, as well as with the corticothalamic apparatus, which resulted in changes in behavior. These consisted of erratic conduct, excitability, restlessness and outbursts of temper and crying.

Neff, Kansas City, Mo.

Some Principles of Child Discipline. R. Miller, Lancet **2**:1469 (Dec. 25) 1937.

Miller disagrees with the "anti-disciplinarians," who regard discipline not merely as something irksome and distasteful, still less as something of teaching and stabilizing value, but as something definitely harmful to children. He defines discipline as the influence exerted on a child with a view to its mental and moral training. At best, discipline is a matter of atmosphere rather than of rules and

regulations, and in this form it has its counterpart in adult life in that vague but none the less powerful influence which is called public opinion. The influence that one exerts, all that is connoted by one's idea of discipline, must aim at guiding the child not only to do but to wish to do and to choose to do what in fact one thinks it well for the child to do. As far as possible rules should be felt as implication—as part of the disciplinary atmosphere rather than hurled at the child as solid facts from which there is no escape. Punishments for children are not, of course, the essence of discipline but rather a sign of failure. It is not easy, however, to get away entirely from punishments, especially in schools, and an important principle involved in them is that the child, at least in time, shall allow in its own mind that the punishment was not undeserved.

"We cannot agree that discipline is in principle harmful for children. It is too much part of Nature's methods, and in children too closely bound up with our protective instinct, for us to admit this. Secondly, we cannot think that complete freedom corresponds with the needs of a child's mind."

LANGMANN, New York.

Diseases of the Genitourinary Tract

ASSOCIATION OF ADENO-MYO-SARCOMA OF THE KIDNEY (WILM'S TUMOR) WITH ARTERIAL HYPERTENSION. J. E. BRADLEY and M. C. PINCOFFS, Ann. Int. Med. **11**:1613 (March) 1938.

Five cases in children are reported in detail. In each child there was a definite increase in blood pressure. In 2 children after surgical removal of the tumors the hypertension promptly subsided; with recurrence of the growths it reappeared.

Analyses were made of the tumor tissue, and in no instance was a pressor substance found.

In the 3 patients who came to necropsy no abnormality of the adrenal glands or urinary back pressure was present. No cause for the hypertension other than the tumor itself was encountered in any of these patients.

Because of the fact that unilateral renal lesions in these children resulted in hypertension the conclusion was reached that the tumor tissue, through an as yet unknown mechanism, had the property of causing abnormal elevation of arterial pressure.

READING, Galveston, Texas.

THREATENED GANGRENE OF THE TESTICLE IN A THREE MONTHS OLD INFANT DUE TO AN INCARCERATED INGUINAL HERNIA. A. TOW, Arch. Pediat. **55**:254 (April) 1938.

A case is reported.

ORR, Buffalo.

MANDELIC ACID IN THE TREATMENT OF INFECTIONS OF THE URINARY TRACT. E. N. COOK, Minnesota Med. **20**:512 (Aug.) 1937.

Cook discusses some of the recent work done in the treatment of urinary infections and gives the results obtained with mandelic acid. He feels that this acid when properly given will produce a biologic reaction that in 90 per cent of the cases of uncomplicated infection of the urinary tract will render the urine sterile. Also, this acid is efficacious in the treatment of complicated infections of the urinary tract and will frequently reduce the number of infections. It is of definite value in the preoperative care of patients. In Cook's experience no permanent ill effects have followed the use of mandelic acid. The desired results can be obtained only if the fluid intake is limited to 1,200 cc. and if the p_H of the urine is 5.5 or below. Cook advocates, however, that during an acute infection with elevation of the temperature the fluid intake should not be limited as long as the temperature remains above normal. When the drug is administered to a patient whose renal function is decreased a careful study of the patient should be made, and if any signs of renal irritation or decreased renal function appear the drug should be discontinued.

ANDERSON, Minneapolis.

OVARIAN TUMORS AMONG YOUNG GIRLS. C. W. MAYO and W. L. BUTSCH, Minnesota Med. **21**:256 (April) 1938.

Mayo and Butsch point out that it is essential to keep the possibility of ovarian tumors in mind when dealing with abdominal symptoms in young girls, and they contend that the occurrence of malignancy in tumors is relatively much more frequent in children than in adults. They describe factors in diagnosis, report cases and suggest an operative technic. Of the 16 ovarian tumors which have been found in young girls at the clinic, one fourth were malignant.

ANDERSON, Minneapolis.

RELATION OF THE CARRIER STATE TO PNEUMOCOCCAL PERITONITIS IN YOUNG CHILDREN WITH THE NEPHROTIC SYNDROME. C. M. MACLEOD and L. E. FARR, Proc. Soc. Exper. Biol. & Med. **37**:556 (Dec.) 1937.

Cultures of material from the nose and throat were made periodically in 12 cases of nephrosis in children from 1½ to 7 years of age, over periods of from one week to two years. The pneumococci isolated from the nasopharynx were typed by Neufeld's technic. In 6 cases in which peritonitis developed the same type of pneumococcus was recovered from both the nasopharynx and the peritoneal cavity.

HANSEN, Minneapolis.

OBSERVATIONS UPON THE MODE OF ACTION AND THE CLINICAL USE OF SULFANILAMIDE IN URINARY TRACT INFECTIONS. P. H. LONG and E. A. BLISS, South. M. J. **31**:308 (March) 1938.

Long and Bliss find that sulfanilamide when properly used constitutes a valuable chemotherapeutic agent in the treatment of infections of the urinary tract. In controlling such infections it seems to act both as a bacteriostatic and as a bactericidal agent. Because of its possible toxic manifestations, it should be employed only after conservative methods of treatment have failed.

SCHLUTZ, Chicago.

VULVO-VAGINITIS IN CHILDREN: CLINICAL AND ADMINISTRATIVE ASPECTS. Brit. M. J. **1**: 961 (April 30) 1938.

This is an editorial comment which sums up a number of other articles. It is general rather than specific; it gives no final information, and no conclusions or deductions are to be drawn therefrom.

ROYSTER, Charlottesville, Va.

PYELITIS IN CHILDREN. E. H. M. STEPHEN, M. J. Australia **1**:485 (March 12) 1938.

Stephen presents a brief discussion of pyuria along usual lines except for any reference to sulfanilamide. He offers the following two prescriptions for use in the acute phases of the disorder as being palatable if not actually enticing: (1) potassium citrate 2.4 Gm. (40 grains), simple syrup 0.6 cc. (10 minims) and chloroform water to 8 cc. (2 fluidrachms); (2) potassium citrate 2.4 Gm. (40 grains), simple syrup 0.6 cc. (10 minims) and compound decoction of sarsaparilla to 8 cc. (2 fluidrachms).

GONCE, Madison, Wis.

KIDNEY GROWTHS IN THE UPPER POLE: AN EARLY DIAGNOSTIC SIGN. R. C. BEGG, South African M. J. **12**:131 (Feb. 26) 1938.

Begg states that the effect of pressure by a tumor of the upper pole of the kidney on the subcostal vein as it passes behind the kidney is seen in a dilatation of the superficial radicals of its anterior branch. This dilatation appears either in the form of a linear vein like a blue pencil mark passing obliquely upward and outward between the anterior superior spine of the ilium and the umbilicus

or as a distinct tracery of small veins at the outer border of the rectus muscle, 2 inches (5 cm.) above the level of the upper margin of the symphysis pubis. At this point there is an anastomosis between the subcostal and deep epigastric systems. This sign appears comparatively early in the course of the development of a tumor of the upper pole of the kidney and is of great value because such a tumor may reach a considerable size before either it or the lower pole of the kidney becomes palpable.

GONCE, Madison, Wis.

LORDOTIC ALBUMINURIA. G. GOLDSCHEIDER, Monatschr. f. Kinderh. **72**:398 (March) 1938.

Goldscheider reports 3 cases in which changes in the electrocardiogram were noted. There were no clinical cardiac abnormalities. The question whether there is any relation between the changed cardiac function and this type of albuminuria requires further study.

GERSTLEY, Chicago.

Diseases of the Ductless Glands; Endocrinology

THE THYROTROPIC HORMONE AND THE ANTIHORMONE PROBLEM. S. C. WERNER, Endocrinology **22**:291 (March) 1938.

Evidence is presented that in guinea pigs a sodium sulfate preparation of the anterior lobe of the beef hypophysis causes refractoriness in a short time, whereas a flavianate preparation continues to produce stimulation for prolonged periods. The conclusion is that refractoriness is an immune response to proteins associated with the active factor in the extracts.

JACOBSEN, Buffalo.

THE SEX HORMONE EXCRETION OF CHILDREN. R. B. OESTING and B. WEBSTER, Endocrinology **22**:307 (March) 1938.

Complete data are given on a colorimetric assay for androgen in urine.

Excretion of androgen and estrogen has been studied in 43 boys and 16 girls. There is a gradual rise in the androgen excreted from early childhood to adult life. At puberty there is a distinct rise in the estrogen excreted. No rise at puberty was found for the androgen. It is suggested that estrogen plays a more significant role in epiphysial closure than androgen.

JACOBSEN, Buffalo.

OBSERVATIONS ON THE QUANTITATIVE ASSAY OF GROWTH-PROMOTING EXTRACT OF THE HYPOPHYSIS. C. CHOU, CHIN CHANG, GRAHAM CHEN and H. B. VAN DYKE, Endocrinology **22**:322 (March) 1938.

The authors give data concerning the assay of the growth-promoting factor of the pituitary.

JACOBSEN, Buffalo.

BIOLOGICAL EFFECTS OF THYMUS EXTRACT (HANSON) ON THYMECTOMIZED RATS. N. H. EINHORN, Endocrinology **22**:335 (March) 1938.

Supplementing the work of Rowntree and his collaborators demonstrating that accruing acceleration of growth occurs when successive generations of rats receive daily injections of thymus extract and that thymectomy retards growth, Einhorn gave thymectomized rats injections of an extract of the thymus.

From observations made on 833 rats distributed in five generations, it appears that the accruing retardation in growth and development incident to thymectomy in successive generations of rats has been not only completely corrected but changed to a moderate accruing acceleration in growth and development by daily intraperitoneal injections of 1 cc. of the aforementioned extract (Hanson).

JACOBSEN, Buffalo.

BIOLOGICAL EFFECTS OF THYMUS IMPLANTATION IN NORMAL RATS. N. H. EINHORN and L. G. ROWNTREE, Endocrinology **22**:342 (March) 1938.

Frequent implantation of thymus in normal rats resulted in accruing acceleration of growth in four generations of offspring. JACOBSEN, Buffalo.

EFFECT OF SYNTHETIC ANDROGEN UPON THE GONADOTROPIC POTENCY OF THE ANTERIOR PITUITARY. J. B. HAMILTON and J. M. WOLFE, Endocrinology **22**:360 (March) 1938.

In the rat administration of synthetic androgenic substance (testosterone propionate) reduced the gonadotropic properties of the pituitary gland. Hamilton discusses the possibility that androgenic material acts to lessen the gonadotropic substance both by suppression of the production of, and by the release of, material stored in the gland. JACOBSEN, Buffalo.

DISTRIBUTION OF BODY WATER AND ELECTROLYTES IN ADRENAL INSUFFICIENCY. H. E. HARRISON and D. C. DARROW, J. Clin. Investigation **17**:77 (Jan.) 1938.

After adrenalectomy rats showed in their serum diminished concentrations of sodium and chloride and increased concentrations of potassium and nonprotein nitrogen. An acceleration of the onset of symptoms of adrenal insufficiency by a high intake of potassium as previously found in dogs, cats and human beings was observed in adrenalectomized rats. The concentration of potassium in the muscle cells was constantly increased in rats showing marked symptoms of adrenal insufficiency, whereas in animals cured of adrenal insufficiency, either by an extract of the adrenal cortex or by a hypertonic solution of sodium chloride and sodium bicarbonate, the concentrations of potassium in the muscle cells were identical with those found in controls (not operated on). No changes in the potassium content of the liver cells were found. In rats with adrenal insufficiency, as well as in control animals, the water content of the muscle cells was inversely related to the concentration of sodium in the extracellular water. GUEST, Cincinnati.

HEPATOMEGALY AND JAUNDICE IN A JUVENILE DIABETIC. R. P. STETSON and W. R. OHLER, New England J. Med. **217**:627 (Oct. 14) 1937.

The importance of the liver in carbohydrate metabolism has been established by many investigators. The author presents indirect evidence favoring the probability that the enlargement of the liver in the diabetic person is caused by fat infiltration. The usual postmortem observations in the livers of young diabetic persons with hepatomegaly have been fatty infiltration and deposits of glycogen within cells and in the nuclei of cells.

The case reported is that of a young boy with diabetes mellitus, hepatomegaly and jaundice from whom a section of the liver for pathologic examination was obtained in the course of an exploratory laparotomy.

Microscopic examination of a section of this tissue stained with Best's carmine showed essentially normal hepatic structure with a tremendous amount of intracellular glycogen.

Recovery from the operation was uneventful. The jaundice subsided in the course of a week. The usual difficulties in regulating the diet and dosage of insulin were experienced just as before the operation.

In general the regulation of the diabetes of this patient was more satisfactory previous to the operation, although he showed frequent glycosuria and acetonuria. Subsequently his diabetes has been severe and usually difficult to regulate, although his liver has not again become enlarged. GENGENBACH, Denver.

USES OF PROTAMINE ZINC INSULIN. W. R. CAMPBELL, New York State J. Med. **37**:1795 (Nov. 1) 1937.

Campbell, of Toronto, gives an excellent review of this subject. A single case of a child, a boy of 15 years, is included among the cases reported. In the treatment of this boy there was a saving of 60 per cent in the amount of insulin required.

AIKMAN, Rochester, N. Y.

EFFECT OF TESTOSTERONE PROPIONATE IN EUNUCHOIDISM. A. T. KENYON, I. SANDIFORD, A. H. BRYAN, K. KNOWLTON and F. C. KOCH, Proc. Soc. Exper. Biol. & Med. **37**:683 (Jan.) 1938.

Four eunuchoids were given synthetic testosterone propionate over variable lengths of time. Enlargement of the prostate, increase in frequency of erections, increase in length of the penis in some, deepening of the voice and progression of other secondary sex characteristics were noted; also, a gain in weight and in nitrogen and sodium retention and a slight increase in the basal metabolic rate were obtained.

HANSEN, Minneapolis.

TREATMENT OF HEPATOMEGALY IN JUVENILE DIABETES MELLITUS WITH A PANCREATIC EXTRACT. H. G. GRAYZEL and L. S. RADWIN, Proc. Soc. Exper. Biol. & Med. **37**:724 (Jan.) 1938.

Three diabetic children who had been suffering from extensive enlargement of the liver for several years were given an alcoholic extract of raw pancreas prepared according to the procedure of L. R. Dragstedt, J. Van Prohaska and H. P. Harms (*Am. J. Physiol.* **117**:175, 1936), and in each instance there was a return to normal size of the liver in from three to five months. Hepatomagaly recurred in from one to two months after the medication was discontinued. The total serum lipids and the lipid phosphorus were lowered with the decrease in the size of the liver.

HANSEN, Minneapolis.

HYPERGLYCEMIC RESPONSE TO HYPOGLYCEMIA IN DIABETIC AND IN HEALTHY INDIVIDUALS. M. SOMOGYI, Proc. Soc. Exper. Biol. & Med. **38**:51 (Feb.) 1938.

The hypoglycemia that follows the hyperglycemia in the dextrose tolerance test in both normal and diabetic persons is interpreted as a delay in the adjustment between the reaction velocities of glycogen breakdown and glycogen formation in the liver. In the diabetic patient the process is greatly magnified, thus the hypoglycemia produced by insulin overdosage causes excessive degrees of hyperglycemia and glycosuria. Recurrence of this sequel over considerable periods of time progressively increases the instability of the patient and aggravates the disease.

HANSEN, Minneapolis.

DYSTROPHIA ADIPOSO-GENITALIS ASSOCIATED WITH HYDROCEPHALUS IN A CHILD AGED TWO YEARS. B. D. CORNER, Proc. Roy. Soc. Med. **31**:358 (Feb.) 1938.

The past history, family history, results of physical examination and of investigations, ventriculograms and pictures of the genitalia of the patient are given.

WILLIAMSON, New Orleans.

ENLARGEMENT OF THE THYMUS IN INFANTS WITH SPECIAL REFERENCE TO CLINICAL EVIDENCE OF SO-CALLED STATUS THYMICO-LYMPHATICUS. A. MONCRIEFF, Proc. Roy. Soc. Med. **31**:537 (March) 1938.

In his article Moncrieff reports the cases of 12 young children who presented various symptoms which appear to be associated with enlargement of the thymus gland as shown in roentgen pictures of the chest. He particularly draws attention

to the less frequent symptom of attacks of a mixture of syncope and dyspnea. His object in giving full reports of these cases was to secure more interest in what may be termed the clinical aspects of thymic enlargement as distinct from pathologic considerations. The condition termed status thymicolymphaticus is out of scientific favor. The condition is diagnosed only after death, as Greenwood and Woods admitted in their paper in 1927. Again in 1931 the pathologic report by Young and Turnbull was concerned with postmortem material in relation to the cause of death. Since the time of these two important contributions roentgenologic evidence has been accumulating, and with this aid it is possible to obtain knowledge as to the size of the thymus gland during life. Moncrieff prefers to range himself with Wright (1937), who in a careful review of the physiology of the thymus gland says in regard to status thymicolymphaticus that the whole subject needs further investigation. He then passes on to consider his 12 cases, giving 7 of them in detail. Next he considers the symptoms that may be associated with thymic enlargement and concludes his paper with comment on the treatment for the condition.

WILLIAMSON, New Orleans.

BLINDNESS OF HYPOPHYSIAL ORIGIN: FOUR CASES OF THE ADIPOSOGENITAL SYNDROME, WITH RETINAL DEGENERATION AND MENTAL BACKWARDNESS. P. PESME and G. HIRTZ, Gaz. méd. de France **44**:833 (Oct. 15) 1937.

Pesme and Hirtz recently studied 4 cases of a curious hereditary and familial syndrome that is characterized by adiposogenital dystrophy, mental backwardness and retinal degeneration. The authors describe these cases not only because of their rarity but because they show the role of the hypophysis in the development of the syndrome, particularly the ocular lesions. The authors direct attention to the similarity of the disorder to the Laurence-Biedl syndrome. The condition in the cases described differs from that designated as the Laurence-Biedl syndrome in the absence of malformations of the members (syndactylism or polydactylism). Three symptoms characterize the typical as well as the atypical forms: obesity of the hypophysial type, mental backwardness and retinal disorders. The retinal symptoms are especially noteworthy: In all cases there was degeneration of the retina, with discoloration and hemeralopia. One of the patients was given extracts of the entire hypophysis for a year, but this form of treatment failed to produce the slightest improvement. After reexamination it was decided to treat the patient with extracts of the anterior lobe of the hypophysis and with several other glandular extracts (thymus, thyroid, adrenals and total hypophysis). Under the influence of this treatment, the patient lost weight and increased in height; moreover, the genitalia developed to normal size; the hands and fingers, which had been extremely short, assumed normal shape, and the nails lost their friability. The mental aspects likewise changed in that the boy became more active and bright. Even more remarkable was the change in the ocular defects. The boy was able to fix his vision without being disturbed by nystagmus, and the photophobia disappeared. Measurement of the visual acuity revealed hardly any increase, but the boy was better able to utilize his visual powers. On the basis of this observation, the authors conclude that the hypophysis influences not only the fat metabolism and the development of the genital organs but also the retina. Such a relationship between the retina and the hypophysis had already been suggested by other investigators, and the authors think that treatment with hypophysial extracts may prove valuable in some congenital retinal defects.

EDITOR'S ABSTRACT. [ARCH. NEUROL. & PSYCHIAT.].

A CASE OF THYMIC DEATH. Y. KAKIZAWA, Acta pædiat. japon. **43**:1761 (Dec.) 1937.

Kakizawa reports a case of thymic death in a boy 1 year 11 months old, with confirmation of the diagnosis at autopsy. The thymus weighed 27 Gm., and histologic examination revealed marked hyperplasia of the lymphoid elements with increased vascularity.

KATO, Chicago.

Diseases of the Muscles, Bones, Joints and Lymph Glands

HODGKIN'S DISEASE WITH TERMINAL EOSINOPHILIA OCCURRING IN A NEGRO CHILD WITH SICKLEMIA. K. KATO and W. W. CARDOZO, J. Pediat. **12**:165 (Feb.) 1938.

Hodgkin's disease with terminal eosinophilia occurred in a 14 year old Negro boy belonging to a family with sickling of the red blood cells. Eosinophilia was absent during the early stages of the disease, although biopsy of a lymph node at that time revealed marked infiltration of the node by eosinophils. This led to the conclusion that the peripheral eosinophilia was the result rather than the cause of the eosinophilia of the node. Evidence points to the possibility that the eosinophils infiltrating the node were not derived from similar cells transported from the bone marrow by way of the blood stream but arose in situ as the result of myeloid metaplasia. The multinuclear giant cells unique in Hodgkin's disease are indistinguishable from normal megakaryocytes in the bone marrow and therefore do not in all probability constitute a distinct strain of pathologic cells but represent a differentiation of reticulum cells under the influence of some pathologic stimulation. These giant cells likely develop in the lymph nodes and have not been transported there from the bone marrow. This interpretation of their genesis in the nodes in Hodgkin's disease adds further evidence as regards the occurrence of myeloid transformation of lymph glands in this disease. On histologic grounds, consisting chiefly of myeloid metaplasia occurring in the lymph nodes, Hodgkin's disease resembles myelogenous leukemia, these two conditions differing in that the blood changes in leukemia are fairly constant whereas in Hodgkin's disease the peripheral blood is scarcely altered. It is suggested that Hodgkin's disease ought to be classed among the diseases of the hemopoietic organs, particularly those involving the lymph nodes and bone marrow, since the characteristic changes are a disorderly multiplication of granulocytes (both eosinophilic and neutrophilic) and of megakaryocytes and lymphocytes, accompanied by fibroblastic proliferation leading to fibrosis—a condition in which, however, the peripheral blood shows no leukemic changes save for a rare increase in circulating eosinophils during the last stage, reflecting the underlying pathologic condition of the involved tissue.

RAUH, Cincinnati. [FROM THE AUTHORS' SUMMARY.]

LUMBOSACRAL ANOMALIES AS A CAUSE OF LOW BACKACHE. W. CLARKSON and A. BARKER, South. M. J. **31**:515 (May) 1938.

Low lumbar pain with or without sciatic radiation is a frequent clinical finding.

Practically all the patients on careful roentgen study will be found to possess one or more lumbosacral defects.

A narrowed lumbosacral disk with subluxation of the lumbosacral articular facets is a more frequent cause of pain than are developmental anomalies.

Herniation of the nucleus pulposus into the spinal canal with pressure on one or more nerve roots is sometimes responsible for intractable low lumbar and sciatic pain.

Osteoarthritic changes are common findings in patients with lumbosacral defects but are thought to represent secondary changes and are not often primarily responsible for pain.

Atypical abdominal and pelvic pain may be caused by low spinal defects, and these should be searched for in patients presenting such symptoms after other possible causes have been excluded.

SCHLUTZ, Chicago.

DISPLACEMENT OF THE INTERVERTEBRAL CARTILAGE AS A CAUSE OF BACK PAIN AND SCIATICA. E. F. FINCHER and E. B. WALKER, South. M. J. **31**:520 (May) 1938.

Cases of pain low in the back with sciatic symptoms are common. The soundest physiologic explanation of the symptoms and findings is obtained in cases in

which a displaced vertebral cartilage can be demonstrated. Such lesions can be accurately localized before operation. The operative risk is minimal, the mortality rate low and the results are most satisfactory. SCHLUTZ, Chicago.

RECURRING ARTHRITIS OF THE HIP, ASSOCIATED WITH ACETONEMIA. D. ENGEL, Edinburgh M. J. **44**:780 (Dec.) 1937.

Engel first described this case of peculiar arthritis in a 3 year old girl in 1924 (*Deutsche Ztschr. f. Chir.* **184**:181, 1924). He now reports her progress after an interval of fourteen years. Always the attacks of arthritis coexisted with episodes of recurrent acetonemic vomiting. Roentgen pictures of the hip joints for both age periods are reproduced. Engel believes the conclusion is warranted that toxic substances, namely acetone bodies present during recurrent vomiting, may have an affinity for articular cartilage analogous to the selection of cartilage and other tissues for pathologic pigmentation in alkaptonuria. In the discussion Engel rules out tuberculosis, osteomyelitis and Perthes' disease.

NEFF, Kansas City, Mo.

A CASE OF FRAGILITAS OSSIUM ASSOCIATED WITH DOLICHOSTENOMELIA. F. SEMAH, Riv. di clin. pediat. **36**:228 (March) 1938.

A girl of 11 years had both fragilitas ossium and dolichostenomelia. The latter condition, also called arachnodactylia, is frequently hereditary and is manifest from birth, being more marked as the child grows older; the head is frequently dolichocephalic, the fingers and toes very long, the muscles hypotrophic and the adipose tissue sparse; congenital malformations of the heart and of the eyes—dislocation of the lens, megalocornea and anomalies of the iris and optic nerve—are not infrequent. The association of these two hereditary diseases suggests a definite etiologic relationship.

HIGGINS, Boston.

Skin Diseases; Allergy

URTICARIA—A NEW THERAPEUTIC APPROACH. H. A. RUSK and B. D. KENAMORE, Ann. Int. Med. **11**:1838 (April) 1938.

Six persons with urticaria were treated by a diet high in protein, low in sodium, with an acid ash, to which potassium chloride was added. All the patients responded satisfactorily to the treatment. The treatment is based on the assumption that in cutaneous irritability and inflammation the metabolism of potassium is altered and that an increase in potassium in the skin causes a decrease in local irritability.

READING, Galveston, Texas.

SODIUM THIOSULPHATE IN THE TREATMENT OF ALLERGY: REPORT OF SIX CASES. J. E. KLEIN, Arch. Pediat. **55**:197 (April) 1938.

A brief series of clinical studies suggests that sodium thiosulfate may be of some value in the treatment of allergic reactions. The drug was used intravenously and orally in the treatment of allergic epilepsy, migraine, urticaria, severe serum reactions and Arthus' phenomenon. The mode of action of the drug has not been clarified.

ORR, Buffalo.

HEREDITARY ECTODERMAL DYSPLASIA. C. G. KERLEY, Arch. Pediat. **55**:211 (April) 1938.

Kerley has observed a case of hereditary ectodermal dysplasia over a period of eight years. The condition is of the anhidrotic, nonsex-linked type. The boy is now 9 years 6 months of age, weighs 59 pounds 6 ounces (27 Kg.) and is 53⅛ inches (135 cm.) in height. His general condition is good. The basal metabolic rate and neurologic observations are normal, and he is of normal mental age.

The lacrimal glands are present and function, and so are the nails of the fingers and toes. There is complete absence of the mammary glands and nipples. Perspiration is absent; the skin is of fine texture and dry. The hair is sparse, of fine texture and has the achromatic characteristics. The eyebrows are absent, and there is just an occasional rudimentary eyelash. There is complete absence of teeth, with poor development of the alveolar processes.

The highest elevation of the body temperature on hot days has been 107 F. The body temperature varies with the outdoor temperature. An outdoor temperature of 90 F. will produce a body temperature of from 102 to 103 F. On moderately warm days the body temperature is from 101 to 102 F. With the outdoor temperature around 60 F., the body temperature will register from 90 to 100 F. The body temperature is increased by physical effort.

The boy's mother had six teeth absent; one maternal aunt lacked eight teeth and another four teeth, which places the patient in the nonsex-linked group.

ORR, Buffalo.

USE OF CALCIUM CHLORIDE IN RELIEF OF CHILLS FOLLOWING SERUM ADMINISTRATION. P. B. BEESON and C. L. HOAGLAND, Proc. Soc. Exper. Biol. & Med. **38**: 160 (Feb.) 1938.

To 13 patients suffering from chills following antipneumococcus serum therapy, a 10 per cent calcium chloride solution was administered intravenously. Complete relief from the chills was noted immediately in most instances. If epinephrine had been given previously the results were not as striking, there apparently being an antagonism between calcium and epinephrine.

HANSEN, Minneapolis.

URTICARIA PIGMENTOSA. R. T. BRAIN, Proc. Roy. Soc. Med. **31**:354 (Feb.) 1938.

An infant of 3 months was noticed to have a pigmented eruption on the trunk at birth. There were many oval or round brown macular lesions, some of which had small papules set in the pigmented spot. The papules were round and firm like those of papular urticaria. Otherwise the skin was normal and the child in good health. The author stated that the eruption was not quite characteristic of urticaria pigmentosa. In any case, the condition is a cutaneous one.

WILLIAMSON, New Orleans.

GRANULOMA ANNULARE. C. E. FIELD, Proc. Roy. Soc. Med. **31**:545 (March) 1938.

Granuloma annulare was reported in a child of 4½ years. Two years previously the buckle of her shoe rubbed her ankle. This appeared to cause a round raised white patch, which gradually enlarged and at the time of the report was growing rapidly. The results of physical examination of the child, the etiologic factors and the treatment are considered in conclusion.

WILLIAMSON, New Orleans.

PERINEURAL SYMPATHECTOMY IN THE TREATMENT OF ULCERS OF THE LEGS. A. B. NOGUEIRA, Arch. de pediat., Rio de Janeiro **10**:331 (April) 1938.

Five illustrative photographs are shown in the same number of cases in which the author obtained good results with this form of treatment. In 1937 there were 103 cases of this condition in children in the Hospital Jesus, in most of which it was due to syphilis.

SANFORD, Chicago.

EXFOLIATIVE DERMATITIS. J. CUPERTINO, J. de pediat., Rio de Janeiro **5**:40 (Jan.) 1938.

The condition was seen in a 24 day old child. The treatment was by application of zinc oxide and injection of 10 cc. of the father's blood. The child died.

SANFORD, Chicago.

A PROPOSAL FOR THE TREATMENT OF FURUNCULOSIS. P. LABIGNETTE, Rev. méd. latino-am. **23**:10 (Oct.) 1937.

The histories of 2 cases of furunculosis are related in which staphylococcic and polyvalent vaccines were without benefit. In both cases the furunculosis cleared up on the administration of small doses, 4 and 8 cc., of insulin daily. The author believes that there is a retention of sugar in the tissues, although it may not appear in the urine.

DWYER, Kansas City, Mo.

Miscellaneous

DIFFERENT CLINICAL GROUPS OF XANTHOMATOUS DISEASES: A CLINICAL PHYSIOLOGICAL STUDY OF TWENTY-TWO CASES. S. J. TANNHAUSER and H. MAGENDANTZ, Ann. Int. Med. **11**:1662 (March) 1938.

In part I of a lengthy article the physiology of cholesterol metabolism is discussed. Part II is devoted to a classification of the xanthomatoses, with presentation of suitable cases and comment descriptive of each type.

The illustrations are excellent, and a complete bibliography is attached.

READING, Galveston, Texas.

EFFECT OF HYPERTHERMIA ON THE DISTRIBUTION OF WATER AND ELECTROLYTES IN BRAIN, MUSCLE AND LIVER. H. YANNET and D. C. DARROW, J. Clin. Investigation **17**:87 (Jan.) 1938.

These studies began with a consideration of the question of why young children are prone to have convulsions at the onset of certain acute febrile diseases. Hyperthermia was produced in cats by exposure to heat for from thirty to sixty minutes. This hyperthermia resulted in a redistribution of water in the brain, involving a shift of water from cells to the extracellular fluid without change in the total amount of water. The concentrations of potassium, nitrogen and phosphorus in the cells increased. The concentrations of sodium and chloride in the extracellular fluid remained unchanged. Confirmation of a shrinkage in cell volume was obtained from histologic examination of the brains of the heated animals. The changes in the brain could be demonstrated in the animals that convulsed as well as those not convulsing as a result of hyperthermia. The same changes could be demonstrated in both young and older animals exposed to hyperthermia. No significant changes were demonstrated in the liver or in the muscle.

GUEST, Cincinnati.

FEVER THERAPY. H. C. SOLOMON and I. KOPP, New England J. Med. **217**:805 (Nov. 18) 1937.

A short review is given of the present status of fever therapy, including descriptions of various methods of induction of fever, such as the production of malaria, the injection of typhoid vaccine or the use of diathermy, luminous-radiant heat or hot, humid environmental air. The clinical applications and results of treatment in a variety of diseases are discussed, and an analysis of the literature is presented.

Excellent results are obtained in: (1) acute gonorrhea and in many gonorrheal complications, including arthritis, epididymitis, orchitis, pelvic inflammation and ophthalmia; (2) neurosyphilis in most of its forms; (3) early syphilis when fever is combined with chemotherapy; (4) late syphilis with symptoms of an inflammatory nature, namely, iritis, interstitial keratitis and periostitis, and (5) Sydenham's chorea. There is a division of opinion as to the value of fever therapy in: (1) infectious or rheumatoid arthritis and other forms of arthritis, (2) chronic asthma and (3) multiple sclerosis. No definite results but interesting experiences are reported from the use of fever therapy in: (1) tuberculosis, (2) subacute bacterial endocarditis and (3) malignant tumors.

GENGENBACH, Denver.

A Simple Inexpensive Method for Concentrating Serum Under Sterile Conditions. W. Thalhimer, Proc. Soc. Exper. Biol. & Med. **37**:639 (Feb.) 1938.

Cellophane in the form of seamless tubes, known commercially as "sausage casings," can be used to concentrate serum to any desired degree. Cellophane can be sterilized in an autoclave at 15 pounds (6.8 Kg.) of pressure for thirty minutes without changing any of its important characteristics. After sterilization of the bag, sterile filtered serum can be added through a glass tube placed in a stopper at one end. The bag with its content may then be placed in front of an electric fan or in a mechanical refrigerator. Evaporation takes place fairly rapidly. In front of an electric fan at room temperature about 1,000 cc. will evaporate at the rate of from 20 to 25 cc. per hour. Small amounts will concentrate more rapidly. Dried serum or concentrated serum can be restored to any volume desired by immersing the bag in distilled water or physiologic solution of sodium chloride. Bacteria will not pass through the intact cellophane membrane, so the redissolved serum will remain sterile. The residue of a small amount of serum (from 10 to 20 cc.) will dissolve under these conditions in from one to two hours.

Hansen, Minneapolis.

Experimental Exchange Transfusions for Reducing Azotemia: Use of Artificial Kidney for This Purpose. W. Thalhimer, Proc. Soc. Exper. Biol. & Med. **37**:641 (Feb.) 1938.

Heparin used as an anticoagulant allowed a dog with both kidneys removed to be given repeated exchange transfusions from a healthy animal. This technic prevented the occurrence of azotemia. Artificial kidneys were made from cellophane bags immersed in physiologic solution of sodium chloride. In nephrectomized animals the heparinized blood was circulated through these cellophane bags and in from three to five hours between 200 and 700 mg. of urea nitrogen passed from the blood into the surrounding physiologic solution of sodium chloride. The possibility of applying this procedure to human subjects is being investigated in collaboration with Prof. C. H. Best.

Hansen, Minneapolis.

Intravenous Benzedrine Sulfate as an Antagonist to Intravenous Soluble Amytal. E. C. Reifenstein Jr. and E. Davidoff, Proc. Soc. Exper. Biol. & Med. **38**:181 (Feb.) 1938.

Ten subjects without apparent disease were given amytal intravenously, and the blood pressure, pulse rate and duration of narcosis were observed in a control period. Several days later the procedure was repeated, and then benzedrine sulfate was given in 10 mg. doses intravenously. In every case narcosis was interrupted.

Hansen, Minneapolis.

The Differentiation of Streptococci and Its Relation to Sulfanilamide Therapy. E. A. Bliss, P. H. Long and W. H. Feinstone, South. M. J. **31**:303 (March) 1938.

Bliss, Long and Feinstone find that recognition of the various kinds of streptococci has an important bearing on the intelligent use of sulfanilamide. Some of these organisms are not susceptible to the action of the drug, and others are not sufficiently pathogenic to warrant the use of this drug. As these differences in susceptibility and pathogenicity are associated with differences in cultural and biochemical reactions, it is possible to determine by easy methods whether or not the use of sulfanilamide is indicated in a given streptococcic infection.

Schlutz, Chicago.

NONSPECIFIC IMMUNOTHERAPY IN PEDIATRICS. E. TOTAFIORE, München. med. Wchnschr. **84**:1207 (July 30) 1937.

This report comes from a children's hospital in Naples, Italy. The good results of the treatment in all children with infectious diseases on whom it has been tried are well known. The author tabulates 385 cases of 12 different acute conditions in which he used a German proprietary preparation. Of 20 cases of sepsis in infants, cures were obtained in 60 per cent. In all other infections the results were better, reaching a high figure of 95 per cent in 150 cases of grip.

BRAHDY, Mount Vernon, N. Y.

PREVENTION OF EARLY DEATHS. O. ROMMEL, München. med. Wchnschr. **84**: 1692 (Oct. 22) 1937.

Although the mortality rate of infants has been greatly reduced, there is still room for improvement, especially during the first four months of life. Better practice of obstetrics is one suggestion. Cooperation between obstetricians and pediatricians in hospitals is necessary, so that the newborn infant may be put under the care of a pediatrician immediately after birth. This is particularly important for those born prematurely (from 10 to 14 per cent of all infants). One difficulty in having infants hospitalized is the refusal of health insurance companies to pay for their care. Rommel writes, "We must insist that the insurance companies pay for the care of these children unless the Führer's words 'All for the Child' are not to remain noise and smoke." The fourth and last suggestion for reducing the mortality rate of infants is that the importance of breast feeding should be stressed. Prospective mothers should be instructed by doctors and midwives, in mothers' schools and through the press and radio.

BRAHDY, Mount Vernon, N. Y.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JOSEPH K. CALVIN, M.D., *President*

Regular Meeting, Oct. 18, 1938

GEORGE F. MUNNS, M.D., *Secretary*

ENZYLAC: A SIMPLIFIED INFANT FOOD. DR. MAURICE L. BLATT and DR. ELLIS H. HARRIS.

During the past year, several hundred infants in institutions have been fed enzylac, a preparation of grade A milk modified by the addition of a pancreatic proteolytic enzyme. Groups of infants ranging in age from newly born to 3½ years were studied. Included with these was a group of premature infants. The growth and development, incidence of infection, blood phosphorus and blood calcium levels, percentage of gram-positive bacilli in the stools and number of stools per day were compared with those of a group of controls. The study was conducted at St. Vincent's Infant and Maternity Hospital and at the Children's Division of Cook County Hospital.

In institutions which have large infant wards, the cost of production of formulas is an important part of the budget. With enzylac the costs of boiling and of subsequent cooling are eliminated. Expensive equipment is not needed, and little time and labor are required in preparation of this food. The diets of the groups studied were identical except for the milk. Cod liver oil and orange juice were added early and cereal, vegetables, puddings, fruit and eggs in the usual sequence.

The conclusions are that the growth and development of infants fed with enzylac compare favorably with those of a reference group. There was a statistically significant difference in the average number of stools per day in the two groups. Only 16 per cent of the infants given enzylac had a single day with five or more stools, while of the control infants 26 per cent had days in which the number of stools was more than five. It is believed that this is a significant index of the superior digestibility of this product. The blood calcium and phosphorus curves of both groups followed normal levels. The hemoglobin and erythrocyte curves of both groups were similar and normal. The experience has proved that enzylac, with its ease of preparation, is a useful base for infant feeding.

DISCUSSION

DR. MAURICE L. BLATT: Because of the multiplicity of infant foods and feeding methods now offered, one introduces a new food or new technic with a good deal of temerity. Enzylac is introduced because its preparation for the infant's formula is safeguarded against overgrowth by contaminating pathogenic bacteria and because of its simplicity of preparation and digestibility.

The boiling of cow's milk for the purpose of making its casein more digestible has proved most useful. Little thought has been given to the coincidental changes produced in the milk. However, the fact that boiling milk makes a great difference in its subsequent bacterial count has not been sufficiently emphasized.

The thermostable bacteria of milk are not killed by pasteurization or by being boiled for three minutes. However, there is reason to believe that these organisms are not only not harmful but probably desirable. However, when milk is heated and it or the equipment used in the preparation of formulas is touched by

human hands or contaminated by bacteria from the upper respiratory tract, the organisms so introduced multiply rapidly in the warm medium. These organisms are pathogenic.

In the preparation of the infant's formula, milk, water and sugar mixtures are commonly used at a temperature somewhat below the boiling point. For several hours after this mixture has been made, this solution remains at a temperature conducive to the rapid multiplication of bacteria which have been introduced during its preparation. It is to do away, so far as possible, with the overgrowth of pathogenic organisms that enzylac is introduced. Its low curd tension makes boiling unnecessary. Milk mixtures suitable for infant feeding can be prepared, therefore, at a temperature optimum for the control of bacterial growth. The milk can be kept in a refrigerator at a temperature of 50 F. Similarly, the sugar solution and the water needed to complete the formula can be added at a temperature of 50 F. The entire mixture therefore at all times has a temperature optimum for the control of bacterial growth.

It is obvious that this process of preparation reduces costs by the elimination of labor associated with boiling milk, of heat units used in raising the milk to the boiling point and of refrigeration used in reducing it from the boiling point to 50 F. or below. In addition, there is greater comfort in the kitchen.

These advantages having been established, there remains only the clinical proof that milk so prepared is a satisfactory food for normal infants of all ages. This fact has been established by the research done by Dr. Harris and myself and reported in his paper.

HYPERPARATHYROIDISM IN CHILDREN: REPORT OF TWO CASES. DR. WILLIE MAE CLIFTON and DR. WILLIAM E. ANSPACH.

A girl now 17 years of age had symptoms which began when she was 9½ years of age and became progressively worse for four years. There were polyuria, pains in the bones, difficulty in walking, multiple fractures, hypercalcemia and hypophosphatemia. Roentgenograms showed generalized osteoporosis and metastatic calcification in the soft tissue. A parathyroid adenoma was removed when the patient was 13½ years old, and to date, three years later, she has had no evidence of recurrence.

A girl now 4 years of age became ill when she was 3 months old with anorexia, failure to gain, bulging of the fontanels, polyuria and pain in the extremities. Roentgenograms showed a generalized severe rachitic-like condition of the bones with acalcification at the ends of the long bones. The skeletal deformities and distortion of the cranium became more marked, and the child became blind when she was 30 months old, before roentgen treatment was begun. Because of the hypercalcemia and hypophosphatemia it is believed that the disease is primary hyperparathyroidism and not renal rickets. After roentgen therapy over the neck the child improved clinically, and the roentgenograms showed increased calcification of the bones.

DISCUSSION

DR. WILLIAM E. ANSPACH: Dr. Clifton gave an outline of the different types of osseous changes pertaining to hyperparathyroidism. The roentgen appearance is suggestive, but one cannot make a diagnosis from this evidence alone. I believe that acalcification is a feature of the condition in younger children. The assumption that acalcification was due to secondary renal involvement was not supported by marked loss in function, a symptom revealed by previously recorded phenolsulfonphthalein tests on older children who showed this change. Certain features are still not clear even after four years' observation, but I believe that in each case the picture is representative of hyperparathyroidism in children. The older patient has the type of osseous changes frequently observed in adults; the other patient was observed at such an early age that her case has no parallel in the literature.

DR. FREDERICK W. SCHLUTZ: The first patient Dr. Clifton reported on was admitted again to the University Hospital a few days ago. The child now shows complete mental deterioration, and there has been progression of all her symptoms, apparently far beyond the degree noted when she was last seen in Dr. Clifton's clinic. Dr. Phemister had great difficulty in finding this tumor. The only parathyroid enlargement present was hardly the size of an extremely small bean. For a few months after the operation the patient showed distinct amelioration of her symptoms, especially a drop in the serum calcium level. The symptoms then returned in an aggravated form. The surgeons are now deliberating whether to operate on the girl again. Her blood serum calcium level is 16 mg. per hundred cubic centimeters.

DR. RALPH H. KUNSTADTER: Is there not a possibility that atrophy of the thyroid has resulted from the frequent roentgen treatments for hyperplasia of the parathyroids?

DR. JOSEPH K. CALVIN: What is the cause of the intracranial symptoms suggesting brain tumor and of the blindness?

DR. WILLIE MAE CLIFTON: As to the question "Is hypophosphatemia the first change in hyperparathyroidism?" Allbright and Ellsworth showed experimentally that hypophosphatemia is the first change due to injection of parathyroid extract.

In reply to Dr. Kunstadter, irradiation for hyperparathyroidism is thought not to produce hypothyroidism. There is no clinical evidence of hypofunction of the thyroid gland in our patient.

In answer to Dr. Calvin's question as to what caused the increased intracranial pressure, I can only say that I do not know.

Book Reviews

Interneships and Residencies: Their Place in Medical Education. Report by the New York Committee on the Study of Hospital Interneships and Residencies. Price, $2.50. Pp. 492, with 83 tables. New York: Commonwealth Fund, Division of Publication, 1938.

A comprehensive study of internships and residencies within New York was made by a thoroughly competent committee representing the five medical schools of New York and the New York Academy of Medicine. The study was made possible by a grant from the Commonwealth Fund. The methods employed in fact finding and in analyzing the data obtained should satisfy the most critical. The report can be taken as accurately descriptive of the conditions which have obtained in New York. The need for an intensive study of this kind had been indicated by findings of the Council on Medical Education and Hospitals of the American Medical Association and by those of the Commission on Medical Education. The report faithfully supplements previous, less intensive and less specific studies. Quite properly it appraises the value of the hospital internship and residency and their place in the general scheme of medical education on the basis of the primary objective of this education, "to satisfy the medical needs of the community."

As an outgrowth of the understanding and the cooperation developed between the medical schools and the hospitals during the progress of the study, the work of the committee is to continue. Therefore, information relative to internships and residencies, as well as to other opportunities for graduate medical education, will be available to those responsible for the guidance of medical students. The definitions presented should be accepted as standard terminology, for the sake of clarity and general understanding.

The report should be of interest to all physicians because of its generally important bearing on the training of future physicians. It has specific importance for those who are medical educators. To pediatric specialists it is of interest because of the place in which pediatrics finds itself in the general scheme of college and hospital training.

Attention is called to the necessity for defining more clearly the relation of the internship and the residency to the basic medical course and to subsequent postgraduate activities. The final test of adequacy is not merely whether the internships and residencies gear satisfactorily into the hospital program but, even more, whether the training received prepares men to become competent and reliable physicians. On these points hinges the efficacy of all proposals to make hospital experience a noteworthy contribution to education. The hospital years are an essential part of medical education and should be so planned.

From the nearly 2,000 physicians responding to the survey it was learned that the proper utilization of hospital resources now available would give adequate training in surgery and obstetrics to approximately the proportion of those who need it in practice. They indicated that with nine tenths of their problems in the home or in the office there was great need for more preparatory training in the outpatient services and that this should have properly organized educational supervision. Other criticisms had to do with lack of essential items of experience, poor quality of teaching in the hospital service and misplaced emphasis. Financial considerations were not looked on as important, being mentioned in only 4 replies. Criticisms were in general concerned with the need for better educational organization of the internships.

It would seem that anything less than a two year internship is inadequate preparation for general practice. Even in a two year internship with six months devoted to medicine, six months to surgery, three to six months to obstetrics and

three or four to pediatrics, there is little time left for such specialties as pathology and anesthesia, except so far as they can be integrated with the regular internships. Although a three year internship would provide a relatively adequate background for general practice, it would seem that for the present the two year internships could be made more effective by a compromise between a straight and a rotating service. This type of training, called a selective internship, is arranged according to the aptitudes and interests of the young medical graduate. By it a physician may be trained to be competent in a limited number of fields. In this form of internship each intern should receive basic training in the care of medical and surgical patients. There a choice of fields would allow opportunity to emphasize a special interest by means of selective assignments in medicine, surgery, pediatrics and gynecology and obstetrics. In addition, time would be available for assignment to outpatient clinics, pathology, the clinical laboratory, anesthesia and other essential phases of training. Such selective arrangements have existed in several of the better New York hospitals for many years; they seem relatively more satisfactory from an educational standpoint.

Of forty-three hospitals with rotating internships of eighteen months or more, thirty-five gave all their interns assignments of less than three months of pediatrics. If one and one-half to two years of rotation cannot provide sufficient pediatric training, the one year rotation is manifestly worse in this respect. The relation between the short assignments and the quality of work was more striking in pediatrics than in any other service. In spite of the importance of a degree of competence in the care of the infant and young child for a physician entering general practice, pediatric training is the weakest part of the preparation given interns.

The problem has been complicated by the number of students who as undergraduates failed to develop a genuine interest in pediatrics. For this reason the importance of the selective emphasis during the internship for those really desiring the experience was more evident in pediatrics than in the other three major fields.

Considered by services, internal medicine was the one providing most complete diagnostic study of all patients admitted and in the teaching of adjuncts to such laboratory work as roentgenography and electrocardiography. The highest score was noted in operating room experience and the lowest in outpatient training.

The pediatric training given in the average rotating internship has a weak position because of the short time usually apportioned to it and because of the interns' lack of interest in the subject. The experience given the interns in pediatric residence and in prolonged special internships has been comparable to that of any other services of like duration.

Residencies have not been so critically examined in the past. By the medical educator they are considered a valuable, if not essential, form of graduate training, serving as they do to bridge the gap between internship and the beginning of the practitioner's career. In spite of this, residencies have not achieved full acceptance as main channels of graduate education. Specialty boards are aiding by defining the fundamental and the specialized training required. Residencies are looked on with great favor by interns, attending staffs and hospital authorities. The duration of the residency should be not less than two years. The main role of this service is to train those physicians who wish to become specialists.

If the resources and standards of residencies could be fostered as suggested, the effect on the whole body of medical education could hardly be overestimated. The change would ease a most serious deficiency, namely, a lack of trained teachers for the instruction and supervision of interns. Curiously enough, little formal effort has been made to qualify a sufficient number of physicians in the art of teaching. To meet this defect, the development of a sufficient number of residencies on a truly educational basis would seem to be the best insurance for future needs. Residents and assistant residents are by the very nature of their duties drawn into the task of supervising and instructing the interns and students. Beneficial to intern and resident alike, habits of teaching are instilled which tend to be life-

long. For this task the residency seems an ideal medium; it should furnish the leaven for vitalizing the whole educational structure.

All thoughtful and forward looking studies of hospital internships and of residencies must arrive at the same conclusion: that their primary and essential function is educational. While they serve a useful purpose in the care of the sick in the modern highly organized hospital, it is only by this practical supervised experience that the student physician can be qualified to assume independent responsibility for the care of patients.

The report is a valuable contribution to fundamental concepts of effective medical training, and its message should not go unheeded.

A Challenge to Sex Censors. By Theodore Schroeder. Price not given. Pp. 159, with 1 illustration. Privately printed to promote the aims of the Free Speech League. New York, 1938.

This book was written by a lawyer who has gathered evidence and arguments against the suppression of "obscene literature." He points out that obscenity is present in the mind of the person who is disturbed and not in the literature. The arguments for the suppression of obscenity are considered analogous to those for the suppression of witchcraft. The whole problem is considered the result of sexual repression in the minds of certain persons. Many quotations from psychiatrists and theologians support the author's opinion.

The arguments are clearly expressed, and the author gives concrete reasons for his point of view.

A Diabetic Primer for Children. By Alfred E. Fischer, M.D. Second edition. Price, 75 cents. Pp. 55, with no illustrations. New York: Alfred E. Fischer, M.D., 1938.

This book aims to give the diabetic child an understanding of his condition, of the place of insulin in treatment and of his food requirements. Many lists of foods are given, with the carbohydrate, the fat and the protein percentages. There is also a discussion of reactions to insulin and of coma.

The book is well written and should be easily understood by any child of high school age, although in my opinion too much attention is given to detail, with insufficient stress on a fundamental understanding of when to expect, how to detect and how to treat diabetic acidosis.

Fettsucht im Kindesalter. By Dr. Richard Priesel and Dr. Leopold Frey. Price, 3 marks. Pp. 44, with 25 illustrations. Stuttgart: Ferdinand Enke, 1938.

The discussion presented in this small volume is based on the authors' experience in a special clinic for the treatment of obesity at the University Children's Clinic in Vienna. The different forms of obesity which occur in children are described, and treatment is discussed. The authors believe that overnutrition is the chief cause in the great majority of such cases, and their treatment is based on this theory. A number of interesting histories and illustrations of patients treated in the clinic are included.

Medicina infantil. By Juan P. Garrhan. Fourth edition. Pp. 1,086, with 214 illustrations. Buenos Aires, Argentina: El Ateneo, 1938.

This is a complete textbook of pediatrics, written in Spanish. The first part of the work deals with the anatomy and physiology of the child, including metabolism, and with the digestive disturbances of newborn and older infants. The second part takes up the various diseases of children, covering the contagious diseases. The chapters on nephritis and nephrosis, on myopathies, and on dystrophies are especially well done. This book is well written and well edited. It compares favorably with any of the standard American textbooks.

Directory of Pediatric Societies*

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Prof. Luigi Spolverini, Policlinico Lungo Tevere Melini 24, Rome, Italy.
Secretary: Professor Vitetti, Rome, Italy.
Place: Boston. Time: Sept. 9-12, 1940.
American Committee:
Chairman: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Kenneth Blackfan, 300 Longwood Ave., Boston.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St., W., Montreal.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

British Paediatric Association

President: Dr. Hector C. Cameron, 23 Devonshire Pl., Upper Wimpole St., London, W. 1.
Secretary: Dr. Arthur G. Maitland Jones, 31A Weymouth St., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialikstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

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* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatría

President: Dr. Clemente Inclan Costa, Manrique 48, Habana.
Secretary: Dr. Serafin Falcon Lopez, Calle B No. 356, Vedado, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincaré, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue du Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Edward Clay Mitchell, 1073 Madison Ave., Memphis, Tenn.
Secretary: Dr. Albert D. Kaiser, 16 N. Goodman St., Rochester, N. Y.
Place: Hotel Chase, St. Louis. Time: May 15-19, 1939.

American Academy of Pediatrics

President: Dr. H. F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary: Dr. C. G. Grulee, 636 Church St., Evanston, Ill.
Place: Netherland Plaza Hotel, Cincinnati. Time: May 16-18, 1939.
Region I. Place: Waldorf-Astoria Hotel, New York. Time: June 1-3, 1939.
Region II. Place: Nashville, Tenn. Time: May 15-16, 1939.
Region IV. Place: Oakland, Calif. Time: April 6-8, 1939.

American Hospital Association, Children's Hospital Section

Chairman: Miss Mabel Binner, Children's Memorial Hospital, Chicago.
Secretary: Winifred Culbertson, Children's Convalescent Hospital, Cincinnati.

American Pediatric Society

President: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid St., St. Louis.
Place: Skytop Lodge, Skytop, Pa. Time: April 27-29, 1939.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. MacGregor, 142 Wellington St., Kingston, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. L. Emmett Holt Jr., Johns Hopkins Hospital, Baltimore.
Secretary: Dr. A. A. Weech, 3975 Broadway, New York.

SECTIONAL

North Pacific Pediatric Society

President: Frederick Fischer, 407 Riverside Ave., Spokane, Wash.
Secretary: Dr. C. L. Lyons, Paulsen Medical-Dental Bldg., Spokane, Wash.

Southern Medical Association, Section of Pediatrics

Chairman: Dr. Charles E. Conrad, 209-210 Professional Bldg., Harrisburg, Va.
Secretary: Dr. Hughes Kennedy Jr., Highland Plaza Apts., Birmingham, Ala.
Place: Oklahoma City. Time: Nov. 15-18, 1938.

STATE

Alabama Pediatric Society

President: Dr. Stewart H. Welch, 1117 S. 20th St., Birmingham.
Secretary-Treasurer: Dr. William R. Britton, 4 Catoma St., Montgomery.
Place: Montgomery. Time: April 17, 1939.

Arkansas State Pediatric Association

Chairman: Dr. G. D. Murphy, 112 Peach St., El Dorado.
Secretary: Dr. Madeline M. Melson, 909 Main St., Little Rock.
Place: Hot Springs. Time: January 1939.

California State Medical Society, Section on Pediatrics

Chairman: Dr. Harold K. Faber, 2341 Clay St., San Francisco.
Secretary: Dr. Hartzel H. Ray, 23–2d Ave., San Mateo.

Florida State Pediatric Society

President: Dr. Gilbert S. Osincup, 300 E. Colonial Dr., Orlando.
Secretary: Dr. Warren W. Quillian, 227 Avenue Aragon, Coral Gables.
Place: Concurrent with state association meeting at time of convention.

Georgia Pediatric Society

President: Dr. Charles Hall Farmer, 553 Walnut St., Macon.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St., N. E., Atlanta.
Scientific Meeting—Place: Augusta. Time: December 1938.
Business Meeting—Place: Atlanta. Time: April 1939.

Hezekiah Beardsley Pediatric Club of Connecticut

President: Dr. C. V. Calvin, 144 Golden Hill St., Bridgeport.
Secretary: Dr. E. T. Wakeman, 129 Whitney Ave., New Haven.
Time: Three meetings a year.

Indiana State Pediatric Society

President: Dr. O. N. Torian, 23 E. Ohio St., Indianapolis.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Morgan J. Foster, 837 Higley Bldg., Cedar Rapids.
Secretary-Treasurer: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.

Louisiana State Pediatric Society

President: Dr. Ruth Aleman, 1407 S. Carrollton Ave., New Orleans.
Secretary-Treasurer: Dr. Philip C. de Verges, 312 Audubon Bldg., New Orleans.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. Paul W. Beaven, 26 S. Goodman St., Rochester.
Secretary: Dr. Leslie O. Ashton, 842 Park Ave., New York.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. John M. Higgins, 600 S. Wilbur Ave., Sayre.
Secretary: Dr. John D. Sturgeon Jr., 22 N. Gallatin Ave., Uniontown.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Allan L. Richardson, 3001 W. Grand Blvd., Detroit.
Secretary: Dr. Ward L. Chadwick, 524 Medical Arts Bldg., Grand Rapids.

Mississippi State Pediatric Society

President: Dr. Guy C. Jarratt, 920 Crawford St., Vicksburg.
Secretary-Treasurer: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Place: To be designated by society. Time: Yearly.

Nebraska Pediatric Society

President: Dr. Herman M. Jahr, 1120 Medical Arts Bldg., Omaha.
Secretary-Treasurer: Dr. Elmer W. Bantin, 440 Aquila Court Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

North Carolina Pediatric Society

President: Dr. W. Myers Hunter, 306 N. Tryon St., Charlotte.
Secretary: Dr. J. R. Adams, 412 N. Church St., Charlotte.

Oklahoma State Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. Ben H. Nicholson, 301 W. 12th St., Oklahoma City.

South Carolina Pediatric Society

President: Dr. Mylnor W. Beach, 126 Meeting St., Charleston.
Secretary-Treasurer: Dr. D. Lesesne Smith Jr., 187 Oakland Ave., Spartanburg.

Tennessee State Pediatric Society

President: Dr. William E. Van Order, 546 McCallie Ave., Chattanooga.
Secretary: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis.
Place: Jackson. Time: April 11, 1939.

Texas Pediatric Society

President: Dr. F. O. Calaway, 3306 Fannin St., Houston.
Secretary-Treasurer: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Place: Houston. Time: May 9, 1939.

Virginia Pediatric Society

President: Dr. W. Ambrose McGee, 616 W. Grace St., Richmond.
Secretary: Dr. John M. Bishop, Medical Arts Bldg., Roanoke.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. J. L. Blanton, 207 Fairmont Ave., Fairmont.
Secretary: Dr. Theresa O. Snaith, 450 Center Ave., Weston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. N. C. Wetzel, 2103 Adelbert Rd., Cleveland.
Secretary: Dr. Fred Rittenger, 10515 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. T. B. Verner, 170 St. George St., Toronto, Canada.
Secretary: Dr. D. V. Hutton, 170 St. George St., Toronto, Canada.

Bronx Pediatric Society

President: Dr. Samuel T. Levethan, 254 E. 184th St., New York.
Secretary: Dr. David Greene, 910 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Benjamin Kramer, 6 Pierrepont St., Brooklyn.
Secretary: Dr. John A. Monfort, 861 Carroll St., Brooklyn.
Place: Kings County Medical Society Bldg. Time: Fourth Wednesday of each month, except May, June, July, August and September.

Central New York Pediatric Club

President: Dr. Frank Vasder Bogert, 111 Union St., Schenectady.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Place: Various cities in New York. Time: Third Thursday of April and September.

Chicago Pediatric Society

President: Dr. Joseph K. Calvin, 2376 E. 71st St., Chicago.
Secretary: Dr. George F. Munns, 723 Elm St., Winnetka, Ill.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Dallas Pediatric Society

President: Dr. W. H. Bradford, 1719 Pacific Ave., Dallas, Texas.
Secretary-Treasurer: Dr. John E. Ashby, 3622 Fairmont Ave., Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. William O'Donnell, 1553 Woodward Ave., Detroit.
Secretary: Dr. Robert Mason, 5140 Second Blvd., Detroit.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatric Section (Atlanta, Ga.)

Chairman: Dr. L. H. Goldsmith, 384 Peachtree St., N. E., Atlanta.
Secretary: Dr. James P. Hanner, 384 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St., N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. John K. Glen, 4412 Montrose Blvd., Houston, Texas.
Secretary-Treasurer: Dr. J. L. Collier, 1620 Medical Arts Bldg., Houston, Texas.
Place: Houston Club. Time: Third Monday of each month.

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385–24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

Kansas City (Missouri) Pediatric Society

President: Dr. Urban Busiek, 200 E. Pershing St., Springfield, Mo.
Secretary: Dr. Fred Speer, 2700 Parallel Ave., Kansas City, Kan.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. H. R. Cooder, 3875 Wilshire Blvd., Los Angeles.
Secretary-Treasurer: Dr. Paul M. Hamilton, 248 E. Main St., Alhambra, Calif.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd.
Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Sidney D. Kramer, 61 Eastern Parkway, Brooklyn.
Secretary: Dr. Benjamin Stoloff, 1149 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: Third Wednesday of each month, October to May.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. James Dobbins, 42-04 Ditmars Blvd., Long Island City, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144–38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Barton Etter, 376 S. Bellevue St., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. Joseph Shimpa, 2309 N. 36th St., Milwaukee.
Secretary: Dr. Helen Jane Zillmer, 781 N. Jefferson St., Milwaukee.
Place: Children's Hospital. Time: Second Wednesday of each alternate month, beginning with February.

New England Pediatric Society

President: Dr. Hyman Green, 483 Beacon St., Boston.
Secretary-Treasurer: Dr. Henry E. Gallup, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Philip M. Stimson, 25 Claremont Ave., New York.
Secretary: Dr. Lucy Porter Sutton, 168 E. 74th St., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northwestern Pediatric Society

President: Dr. Robert Rosenthal, 437 Lowry Medical Arts Bldg., St. Paul.
Secretary-Treasurer: Dr. R. E. Nutting, 205 W. 2d St., Duluth, Minn.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. A. L. Salomon, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 1200 N. Walker St., Oklahoma City.
Time: Every month, except June, July and August.

Philadelphia Pediatric Society

President: Dr. Julian M. Lyon, 40 Llanfair Rd., Ardmore, Pa.
Secretary: Dr. Aims C. McGuinness, Children's Hospital, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday of each month from October to April, inclusive.

Pittsburgh Pediatric Society

President: Dr. James LeRoy Foster, Highland Bldg., Pittsburgh.
Secretary-Treasurer: Dr. E. R. McClusky, 3200–5th Ave., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate months from October to June, inclusive.

Richmond Pediatric Society

President: Dr. A. S. Hurt, 1028 W. Franklin St., Richmond, Va.
Secretary-Treasurer: Dr. Louise Fry Galvin, 2416 Stuart Ave., Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: First Thursday of each month, except July, August and September.

Rochester Pediatric Society

President: Dr. J. Merrel Parker, 11 N. Goodman St., Rochester, N. Y.
Secretary: Dr. H. C. Soule, 16 N. Goodman St., Rochester, N. Y.
Place: Arranged by program committee. Time: Second Friday of each month.

Rocky Mountain Pediatric Society

President: Dr. John Schoonover, Republic Bldg., Denver.
Secretary: Dr. F. Craig Johnson, 1850 Gilpin St., Denver.
Place: Children's Hospital, Denver. Time: First Saturday of each month from September to May, inclusive, 7:30 p. m.

St. Louis Pediatric Society

President: Dr. John Zahorsky, 536 N. Taylor Ave., St. Louis.
Secretary-Treasurer: Dr. Max Deutch, 634 N. Grand Blvd., St. Louis.
Place: St. Louis Medical Society. Time: Third Friday of every month.

Seattle Pediatric Society

President: Dr. Jay I. Durand, 1305–4th Ave., Seattle.
Secretary: Dr. Frederick B. Joy, 1215–4th Ave., Seattle.
Place: College Club. Time: Third Friday of each month, 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Philip E. Rothman, 3875 Wilshire Blvd., Los Angeles.
Secretary: Dr. Norman Nixon, 1136 W. 6th St., Los Angeles.
Place: University Club of Los Angeles. Time: First Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Clement Smith, 1101 Beacon St., Brookline, Mass.
Secretary: Dr. D. Murray Cowie, University of Michigan, Ann Arbor, Mich.
Place: Horace H. Rackham Graduate School, Ann Arbor, Mich. Time: Nov. 11-12, 1938.

Westchester County Medical Society, Pediatric Section (New York)

President: Dr. Norman Survis, 650 Main St., New Rochelle.
Secretary-Treasurer: Dr. Elvira Ostlund, 131 Purchase St., Rye.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

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